

MODERN THERAPEUTICS

THE PRACTITIONER HANDBOOKS

Edited by SIR HUMPHRY ROLLESTON, Bt., G.C.V.O., K.C.B.,
M.D., F.R.C.P., and ALAN A. MONCRIEFF, M.D., F.R.C.P.

FAVOURITE PRESCRIPTIONS
PRACTICAL PROCEDURES
MODERN ANÆSTHETIC PRACTICE
DIET IN HEALTH AND DISEASE
MODERN DIAGNOSIS

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EDITORIAL PREFACE

THE contributions to this book have all appeared in THE PRACTITIONER during the past two years, but every chapter has been revised, sometimes extensively, and every author has been encouraged to make whatever alterations and additions seemed necessary to bring his section up to date. The developments of modern therapeutics are often so rapid that such revision was essential, and it was, in fact, just such rapid change and increasing complexity in so much of modern drug treatment that led to the planning of these articles. It has become almost impossible for any one expert to possess detailed knowledge of therapeutic advances in every direction, and hence a particular advantage of 'multiple authorship' is to be found in the pages which follow. In some instances the subject has been entrusted to a laboratory worker, in others to a clinician, and in some to an individual fortunate enough to be a pharmacologist with concurrent clinical experience. It is hoped that in this way each chapter has secured for its authorship the best authority available.

This volume is not a comprehensive treatise on therapeutics: subjects have been chosen sometimes because of recent and important developments and sometimes because, although the drug is old and familiar, it is not always used to its best advantage. An example of the latter is to be found in the chapter on digitalis and of the former in the section dealing with the modern treatment of malaria.

The sulphonamide group of drugs is not described here in detail as a separate chapter, although fully mentioned as regards the value of each member of the group as a urinary antiseptic, for example, in Chapter XI, because finality on this subject has by no means yet been reached and there is already available a PRACTITIONER BOOKLET (*Essentials of Modern Chemotherapy*) which covers the ground.

While this volume was being prepared for the press the

EDITORIAL PREFACE

Therapeutics Requirements Committee of the Medical Research Council published an important memorandum on "Economy in the Use of Drugs in War Time" (H.M. Stationery Office, price 3d.). It was felt that to revise the whole book along the lines recommended in this pamphlet would narrow its value, particularly when normal conditions are restored. Accordingly the drugs chosen by authors have been allowed to stand, but before prescribing any of the drugs mentioned in the text readers are advised to consult the list of substitutes or equivalents printed as an appendix to this book (p. 321).

The editors are glad to have this opportunity of thanking all those who have contributed to this book, for their pains-taking revision and close cooperation in setting out the latest and most accurate knowledge available on drugs in the everyday use of most general practitioners.

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CHAPTER I

THE ADMINISTRATION OF DRUGS

By the late A. J. CLARK, M.C., M.D., F.R.C.P., F.R.S.
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CHAPTER I

THE ADMINISTRATION OF DRUGS

DURING the present century the general trend of therapeutics has been to use fewer drugs but to employ those used in doses adequate to produce a definite therapeutic effect. This tendency has necessitated a much closer study of the margin between the therapeutic and toxic doses. The more intensive use of drugs has also made necessary the accurate standardization of drugs, and this has led to the development of methods of biological standardization for those drugs, the activity of which cannot be estimated by chemical methods.

One of the results of the study of biological standardization has been to reveal a hitherto unsuspected range of individual variation in animals as regards their response to drugs. Such studies on healthy animals, frequently of inbred stock and uniform as regards age and sex, have shown that in any hundred individuals there is rarely less than a four fold range in the doses needed to produce similar effects in the most sensitive and least sensitive. This scatter is greater when mixed stocks are used, moreover, it differs with different drugs and in some cases is much greater than that mentioned.

The variation of human patients is a familiar fact, but it is difficult to obtain a quantitative estimate of its extent. The evidence available indicates that the variation is usually greater in human patients than in animals. This is to be expected, because the former vary as regards age and sex and also are affected to varying extent by disease.

MARGIN OF SAFETY

The existence of human variation in response to drugs makes it necessary for therapeutic methods to permit the adjustment of the dose of drug given to the individual need of the patient. Rules for the adjustment of dosage to age, sex, and weight

may be useful but they do not eliminate the difficulty of individual variation. As a general rule the range of individual variation in a group of moderate size is similar in extent to the range between the therapeutic and toxic doses of drugs. Hence it is impossible to calculate a dose which will be adequate for all patients and yet toxic to none. Only those methods are safe which begin with a moderate dose and permit the dose to be increased in accordance with the requirements of the individual.

The problem of the margin of safety of drugs has been studied particularly carefully in the case of chemotherapeutic agents. Ehrlich wisely insisted on the necessity of a wide margin of safety. Fortunately this is a question that can be determined by animal experiments, only those agents are introduced into therapeutic use which are satisfactory in this respect and, in general, the question of safety of single doses of drugs has been studied with considerable care.

DURATION OF ACTION

In the case of the great majority of drugs it is necessary to produce a nearly constant effect for an adequate time, and to obtain this result it is necessary to know the rate of absorption and clearance of drugs, since upon these factors depend the duration of action of a single dose, the frequency of dosage needed to maintain a desired effect, and the extent to which cumulation will occur.

The duration of action of drugs has been studied much less extensively than the relation between dosage and the intensity of the effect produced. As a result drugs tend to be administered three times a day after meals without much question whether or not this method is the most suitable form of administration.

As regards the absorption of drugs from the alimentary canal the following general facts are of importance:

Little absorption occurs from the stomach, and hence the rate of absorption depends on whether the stomach is full or empty. For example, when a moderate quantity of dilute alcohol is taken on an empty stomach half is absorbed in about twenty

minutes and absorption approaches completion in an hour. The presence of food in the stomach about doubles these times. The absorption of most drugs from the gut is slower than that of alcohol because the latter is exceptional in that it is absorbed to a certain extent from the stomach.

CLEARANCE OF DRUGS

The chief methods of removal of drugs from the circulation are urinary excretion and inactivation by the liver. Both these processes usually follow an exponential course, that is to say a constant fraction of the drug present in the body is removed per unit of time. Alcohol is the only important exception to this rule and, in this case, the quantity oxidized per minute is constant and does not vary with the amount present in the body. The exponential clearance of drugs has certain important consequences as regards duration of action and cumulation. The cumulation produced by drugs which are excreted in an exponential manner is easy to calculate. If the drug is given in constant doses at a constant interval and a fraction (e.g. $1/10$) is cleared in the interval, then cumulation will continue until clearance balances intake. This will occur in the case mentioned when $1/10$ of the amount in the body equals the single dose. Hence in this case the amount cumulating in the body will be ten times the amount given in a single dose.

The influence of these facts on the mode of administration of drugs can best be shown by considering a few important cases. Salicylates and digitalis are examples respectively of drugs that are rapidly and slowly excreted, whereas iron provides an example of a drug that can be stored in the body.

The treatment of rheumatic fever with sodium salicylate is an example of a case in which it is necessary to maintain a steady concentration of drug in the body (10 to 20 mgm per 100 c.c.m.) for several days. The rate of excretion of salicylates in rheumatic fever is about $1/30$ per hour of the drug present. If the drug is given four hourly, then about $1/9$ (11 per cent) of the drug in the body is excreted in each interval. A dose of 1 gramme four hourly will cause a cumulation of 9 grammes.

in the body (14 mgm per 100 c.c.m in 70 kgm individual). The amount of drug present when full cumulation has occurred will be 9 grammes shortly after a dose and this will fall to 8 grammes before the next dose. This calculation does not allow for the delay due to absorption, which will reduce the fluctuation somewhat. If it were desired to maintain the salicylate in the body above 8 grammes by means of doses twice a day, then 4 grammes doses twice a day would cumulate to provide 12 grammes in the body immediately after the dose and 8 grammes immediately before the dose. The daily dosage would be the same as before, but the fluctuations in concentration would be much greater and the maximum concentration produced would be much more likely to produce toxic effects. If the drug were given daily, then 50 per cent would be excreted between doses and a daily dose of 8 grammes would be needed to cumulate to 16 and 8 grammes in the body before and after the doses. These calculations are based on chemical estimates of the excretion of salicylates and they show clearly that the only satisfactory method of maintaining a steady concentration in the body is to give frequent doses by mouth. Massive intravenous therapy would be obviously unsuitable in this case because it would produce toxic effects for a short period, and the rapid clearance of the drug would cause the concentration to fall to an inactive level within one or two days.

The sulphonamide group of drugs resembles the salicylates as regards distribution in the body and rate of excretion, and the principles mentioned above would appear to apply equally to the sulphonamide drugs.

Frequent oral administration is much the simplest method of maintaining a steady concentration of any drug that is rapidly cleared from the body. When this method is impracticable the best alternative is to give subcutaneous or intramuscular injections in some form that is slowly absorbed. Protamine zinc insulin is a typical example of this type of therapy.

Digitalis provides a striking contrast to salicylates in that it is slowly excreted and cumulation is the most important

feature in its administration. The rapid effects produced by intravenous injections of strophantidin or digoxin prove that the action of these drugs is rapid once they attain an adequate concentration around the heart. The fate of digitalis glucosides cannot be determined by chemical tests, but estimates of its rate of clearance have been made from the rate of change in clinical symptoms when the drug is stopped. Estimates of this type indicate a loss of from $1/10$ to $1/20$ of the drug present per diem, which is an exceptionally slow rate of clearance. The amount of tincture needed to produce a full therapeutic effect varies widely in different patients, but 20 c cm (300 minims) is a common value for the total amount required to produce a full clinical response when the drug is given intensively within two or three days. If $1/10$ is cleared per diem, then a daily dose of 2 c cm (30 minims) will ultimately (after two or three weeks) produce a cumulation of 20 c cm in the body, and thereafter this quantity will remain constant, provided the dosage is constant. If intensive therapy is used the effective cumulation will be produced much more quickly, but the maintenance dose needed to maintain the cumulation will be the same as with gradual therapy, namely 2 c cm .

The results of these calculations are in general agreement with clinical experience but it must be noted that there are many factors which may cause irregular response. For example, the absorption from the gut in a case of acute heart failure is seriously deranged and will improve as the circulation improves, hence a constant dosage may cause an increasing effect when the patient begins to improve.

It is of interest to note that the rate of clearance of digitalis is so slow that the frequency of dosage is not important and the effect depends upon the total dose received daily.

Bromide is another example of a drug which can cumulate until it produces toxic symptoms. The kidneys excrete bromides and chlorides in the proportions in which they occur in the plasma. The body fluids contain about 150 grammes of sodium chloride, whilst 119 grammes of potassium bromide replace 58 grammes of sodium chloride. If 3 grammes of potassium bromide and 10 grammes of sodium chloride are

taken daily, then $1/13$ of the bromide will be excreted daily and the bromide will cumulate until the body contains 31 grammes of Br, which quantity will produce a blood concentration of about 150 mgm Br per 100 c cm of plasma. Concentrations of blood bromide above 100 mgm per 100 c cm are liable to produce toxic actions. The dose of bromide mentioned will take three weeks to raise the blood concentration to 100 mgm per 100 c cm and two months to raise it to 150 mgm per 100 c cm. These figures indicate the slow and insidious manner in which bromide intoxication is established.

BODY STORAGE

The two examples already discussed are relatively simple. In the case of both salicylates and digitalis it is first necessary to establish an effective concentration of the drug and then to maintain this by a maintenance dose. The chief variable is the rate of excretion, if this is rapid, as in the case of salicylates, frequent dosage is essential, whereas this is not essential with the slowly excreted digitalis.

Substances which can be stored in the body present a more complex problem than those considered previously. Iron and ascorbic acid are two examples of substances of which the body normally maintains a considerable reserve store. The body contains from 3-5 grammes of iron, and about two-thirds of this is in combination with haemoglobin in the blood, one-sixth is distributed throughout the body as tissue iron and one sixth forms a reserve store in the liver and spleen and bone marrow. If iron deficiency occurs the tissue iron is not affected but the reserves are exhausted and the amount of haemoglobin is reduced. In the treatment of anaemia with iron it is therefore necessary not only to supply iron for the formation of more haemoglobin but also for the refilling of the depleted reserves. This is one reason why successful iron therapy requires doses of iron greatly in excess of the amount needed for the replacement of the deficiency in haemoglobin.

Ascorbic acid provides a striking example of a necessary substance of which the body maintains a store greatly in excess of its current needs. In one study made on a healthy adult

almost complete deprivation of ascorbic acid for six months only produced slight signs of deficiency during the last month, but a subsequent saturation test showed that the subject had incurred a deficiency of about 5 grammes of ascorbic acid. The daily need of ascorbic acid is about 30 mgm and a well-nourished body appears to contain a mobile reserve adequate for about six months usage. The implication of this fact is that deficiency of ascorbic acid will not produce scurvy until a very extensive depletion has occurred, and prolonged and massive dosage will be needed to restore normal conditions.

The quantities of different vitamins held in reserve by the body vary in a remarkable manner. There are large reserve stores of ascorbic acid and of vitamin A, whereas the reserves of thiamin and of vitamin K appear to be sufficient to cover a few days usage only.

The treatment of deficiencies that imply the depletion of relatively large reserve stores is a complex problem. Small doses are likely to cover current needs and to relieve urgent symptoms, but far larger doses will be needed to replenish the depleted stores and to bring the body to a normal condition.

SUMMARY

The three examples discussed illustrate a diversity of therapeutic problems. In the case of drugs which are rapidly excreted the problem is how to maintain an adequate concentration of drug in the body, without ever raising this concentration to a toxic level. The most effective way of doing this is to give frequent doses by mouth. Sodium salicylate and the sulphonamide drugs are examples of this form of therapy. In the case of drugs that are slowly excreted, such as digitalis, the frequency of dose does not matter, and the total daily dosage is the point of importance, but in this case the laws regulating cumulation are very important. A large initial dosage (e.g. 20 c cm tincture in three days) followed by 2 c cm a day will maintain a body content of about 20 c cm, on the other hand the administration of 2 c cm a day without any large initial dose will ultimately work up to the same amount, but this will take two or three weeks. Drugs which are slowly

excreted, and hence tend to **cumulate**, obviously present special dangers. The chief drugs with a markedly cumulative action are digitalis, thyroid, bromides, mercury, and arsenic.

A third group of drugs is characterized by the fact that the body holds them in the form of stores or reserves. When these drugs are given to relieve deficiency it is necessary to fill up the depleted reserves, hence the amounts required are disproportionately large in comparison with the known daily needs for maintenance. Iron and calcium are two examples of such drugs, and some of the vitamins also behave in this manner.

CHAPTER II

THE THERAPEUTICS OF DIGITALIS

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CHAPTER II

THE THERAPEUTICS OF DIGITALIS

THE intelligent use of digitalis has been claimed as one of the major triumphs of modern therapeutics, but brilliant results can seldom be achieved by the haphazard and indiscriminate use of this or any other drug. The digitalis bodies form such potent remedies in the treatment of selected forms of heart failure, that it is as desirable to define the indications for their use as it is to appreciate the guiding principles in their successful employment. It is recognized that the patient is likely to reap maximum benefit when an adequate quantity is administered as quickly as his symptoms demand, and the effect maintained, even indefinitely, without the production of intoxication. Digitalis has its limitations. To offer it to all and sundry, even in short measure, for this or that complaint, is a confession of failure which reflects sadly on the outlook of the practitioner. The error is all the greater when, with intensive and controlled therapy under appropriate conditions, so much of value may be readily accomplished.

For practical purposes it is useful to consider digitalis medication under two headings—the *digitalizing* dose, by which is meant the amount required to produce a full therapeutic response, and the *maintenance* dose, which is the quantity of the drug necessary to perpetuate and sustain the preceding digitalization with optimum benefit to the patient. The former dose is in fact an amount of the drug just short of that quantity which induces symptoms of intoxication. With few exceptions, the mildest symptoms of digitalis poisoning, such as headache and loss of appetite, are a better guide to adequate digitalization than the rate of the pulse or the amount of cardiac slowing induced by the drug.

The digitalizing dose varies for different patients, and although it is possible to foretell roughly the total quantity

required to produce maximum benefit yet this can only be determined in practice by the method of trial and error. If the patient is to receive full benefit over lengthy periods of time, as is so often desirable, maintenance dosage requires the most careful regulation. It is regrettable that this aspect of digitalis therapy should have received less attention than it merits. With doses too small to be really effective digitalization may never be attained. On the other hand maintenance dosage, after the effective quantity has been determined, may be so poorly controlled as to result in a failure to preserve full digitalization for a sufficiently long period or, doses being too large, symptoms of intolerance may be induced. In either instance, the patient is disappointed and discouraged.

THE DIGITALIZING DOSE

A patient who has not taken any of the digitalis group of drugs in the preceding fourteen days can safely tolerate an unusually large dose. Admittedly, there are individual variations—some patients tolerating more, some less, than the average quantity—but as a general rule, clinical experience teaches that advantage can be taken of the fact that a full saturation dose depends chiefly on the weight of the patient and the potency of the preparation used.

For example, a man of 140 pounds requires on a theoretical basis a total of 21 c cm of the standard B P tincture in the course of twenty four hours to produce a full saturation effect. It is not suggested that the digitalizing dose should be calculated for each patient requiring the drug although this can be done quite simply according to the formula devised by Eggleston who found that 0.15 c cm of a standard tincture (1 cat unit per c cm) per pound body weight was the average dose required to produce full effects. A patient of 140 pounds will therefore require $140 \times 0.15 \times 1 = 21$ c cm of a standard tincture or 210 grammes of the powdered leaf. In using this method the total quantity thus determined is administered in suitable fractions over a period of twenty four hours. For this purpose the tincture is particularly suitable as the doses can be readily measured and administered at six hour intervals beginning with half the total (say 10 c cm or 150 minims) followed by one quarter or a trifle more (say 6 c cm or 90 minims) followed by 3 c cm (45 minims) and 2 c cm (30 minims), each at intervals of at least six hours. The nurse who does not have a medicine glass graduated in the metric system can

easily measure the dose of the tincture in a record syringe. If the principle be appreciated that a man of 10 stone requires as much as 21 c.cm or rather more than 300 minimis of the tincture in twenty-four hours to produce full effects then the practitioner may make use of bolder doses than those commonly employed to secure rapidly the beneficial effect of full digitalization.

The method is safe and can be thoroughly recommended whenever digitalis is urgently required, but it must not be employed if digitalis or an allied drug has been taken within the previous ten or fourteen days, as serious toxic effects may then follow the first fraction of the massive doses. The patient requires particular observation over the period of administration of the drug and the attendant should be instructed to discontinue further doses on the first appearance of headache, anorexia, or nausea. When a patient has not been treated recently with digitalis, half the total calculated quantity may be administered without the slightest misgiving. It is the later fractions in the series which require particular care in their use. Symptoms of intoxication are more likely to occur after the second, third, or final dose, but even on certain occasions further doses in excess of the calculated theoretical requirements may be continued for several days before the first signs of over-saturation make their appearance. The nurse should be instructed to stop the administration of the drug on the first appearance of intolerance. Vomiting, having been preceded by the earlier and milder symptoms of intoxication, is a certain indication that too much of the drug has been administered. Vomiting should not be allowed to occur. It distresses the patient unnecessarily, and by the retching induced, which may persist for twenty-four hours or more, imposes an unnecessary and undesirable burden on his circulatory system. Moreover, should maintenance doses prove to be desirable at a later date, the patient will naturally be prejudiced against its further use.

The fact that certain individuals have a remarkable tolerance for digitalis is demonstrated in fig. 1. This patient received a dose of 32 c.cm in twenty-four hours in suitable fractions, calculated on his body-weight, with prompt and remarkable benefit. After an interval of two days he took 30 minimis of the tincture thrice daily for six days, before the

first symptoms of intoxication appeared. To tolerate such a large quantity is exceptional, but it does indicate the safety of the method and the importance of continuing the drug until full benefit is obtained, provided always that the patient is

DAYS

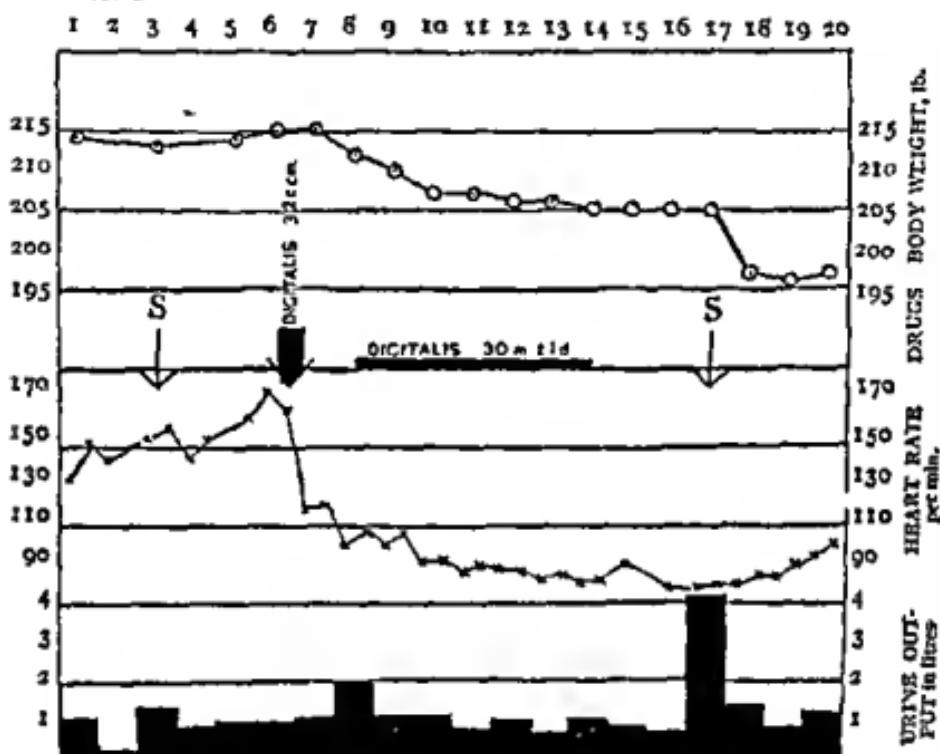


FIG. 1.—To show the effect of massive doses of digitalis tincture in a man, aged 46, 215 lb in weight, suffering from congestive heart failure with auricular fibrillation. He received successively 15 c.c.m., 8 c.c.m., 5 c.c.m., and 4 c.c.m. at intervals of six hours on the sixth day of observation without the production of intoxication. He had a remarkable tolerance for the drug, as two days later 30 minimis was begun thrice daily and continued for six days, when nausea was first induced. A fall in body weight amounted to 10 lb. It is noteworthy that digitalis potentiates the effect of salyrgan (S). Compare the effect on body-weight and urine output of the dose of 20 c.c.m. on the third day with that on the seventeenth, when the man had been digitalized.

kept under observation and the dose regulated by careful consideration of his symptoms.

The method briefly outlined above is the natural outcome of the observation that 20 or even 30 minimis of the tincture may commonly be taken thrice daily for from seven to ten days, at

the end of which time the first symptoms of digitalis poisoning may be observed. By doubling this dose, the time lag is reduced to between four and five days, and by trebling the dose, the same effect can be obtained in one or two days. The quantity administered and its rate of absorption are the important factors in determining the response. At least six hours elapse before a dose is absorbed and becomes fully effective. Hence the wisdom of allowing such an interval to elapse between successive large doses. When digitalis is indicated it is desirable that its beneficial action should be achieved quickly, not merely for the comfort of the patient, but the prompt response thus induced will frequently clarify the situation for the practitioner and facilitate further treatment. When the state of the circulation demands its employment, there is nothing to lose and much to gain by early adequate digitalization. A patient appreciates bold measures, when these are based on reason and purposely designed to restore health and comfort as rapidly as possible.

In general practice, a bottle of 1 or 2 oz. of the pure tincture is often sufficient for the immediate purpose. To produce digitalization reasonably quickly, as a general routine, 120 minims—diluted in water immediately before use—may be ordered as a first dose and, six hours later, in the absence of headache and nausea a further 60 minims, and after a similar interval 30 minims may be taken. In hospitals, or nursing homes, where greater resources are at hand, more accurate methods may be employed and the dose calculated in c cm of the tincture, suitable fractions being administered according to the method outlined above. If the fractions—either in c cm or in minims—have been successfully tolerated, then it is desirable to continue smaller doses, say of 30 minims, twice or thrice daily, until a definite relief of symptoms is obtained or until the first distinct symptoms of intoxication make their appearance. The administration of the drug is then discontinued for at least two days. It is at this stage that the patient may be said to be fully digitalized. The circulatory response, thus rapidly induced, at once gives a clue both to the prognosis and to the desirability of further therapeutic measures.

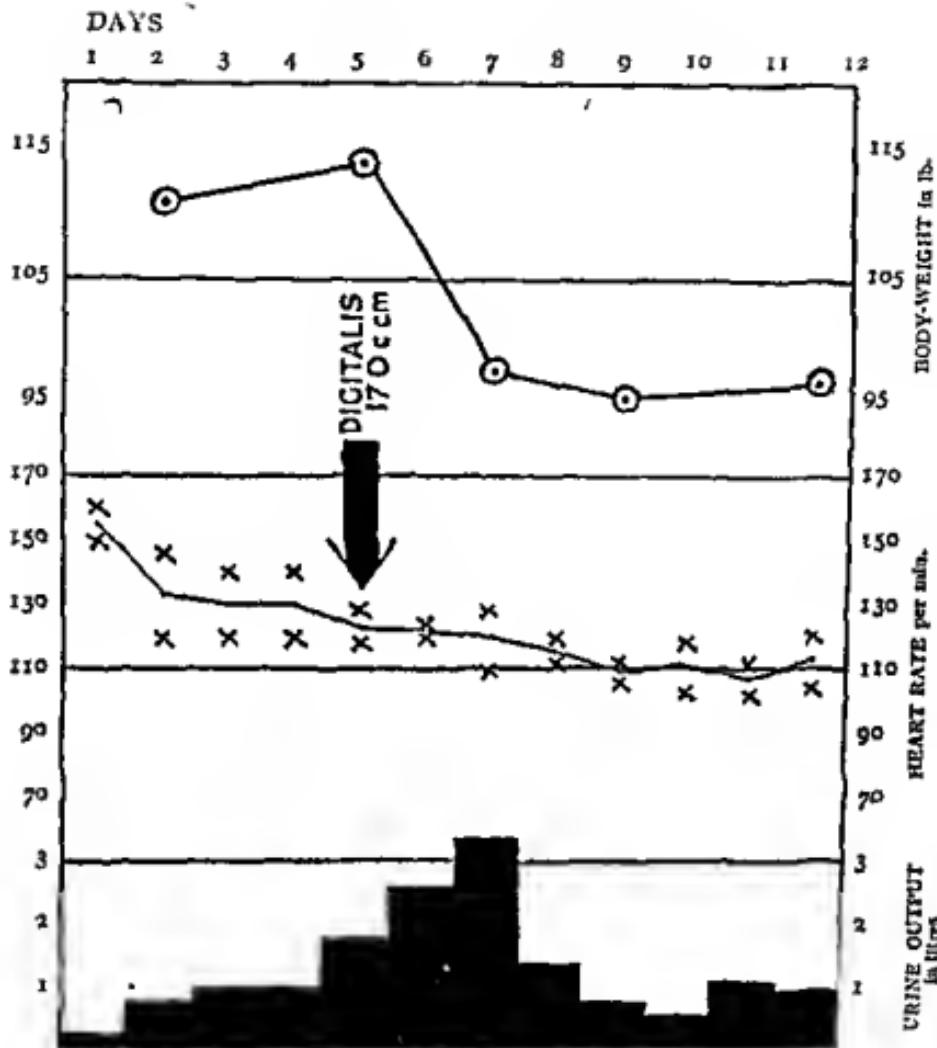


FIG. 2.—To show a prompt response to massive doses of digitalis without a significant slowing of the heart rate. The patient suffered from thyrotoxic heart disease with normal rhythm and congestive heart failure. 17 O cm of digitalis tincture in suitable fractions over twenty-four hours induced a profuse diuresis, and within forty-eight hours, a fall of 16 lb in body-weight. The maximum and minimum heart rates for each day are charted; the continuous line indicates the average daily rate. A gradual slowing in rate, amounting to 10 beats per minute, was observed after the diuresis had subsided, and after the patient had obtained relief from her circulatory distress.

In the treatment of congestive failure there is no drug to compare with digitalis. Within twenty-four or forty-eight hours of complete digitalization remarkable benefit may be observed. Sleep becomes more restful and more readily

obtained, dyspncea lessens, diuresis begins, the body-weight falls, and the venous pressure decreases. These are all obvious effects, which can be readily observed and recorded from day to day, but the increased bodily comfort and the restoration of a sense of well being are none the less real, although they defy accurate analysis. As a guide to the efficacy of digitalis therapy, records of body-weight are more helpful than the chart of the heart rate (fig 2). The rate of the heart is not a measure of the therapeutic response. The importance of slowing of the heart has been over-emphasized, although in cases of auricular fibrillation, with a fast ventricular rate, this may be dramatic (fig 3). When normal rhythm accompanies congestive heart failure, digitalis can act with full benefit without any appreciable alteration in the rate of the ventricles, or with a decrease so slight—perhaps no more than ten or twenty beats per minute—as to have little or no influence on the therapeutic response (fig 2).

MAINTENANCE DOSAGE

Having secured full digitalization and having noticed particularly the response of his patient to this procedure, the practitioner will then decide on the necessity for a continuation of the full digitalis effect. It is wise to explain the procedure to the patient, so that his full cooperation may be enlisted from the start. Too frequently, the patient misinterprets the practitioner's intentions and is loath to resume the administration of a drug of which he may believe himself to be intolerant.

The aim in maintenance doses is to perpetuate a concentration of digitalis in the tissues, just short of that amount which is capable of inducing intoxication. The secret of success is to be found in the use of the drug in short intermittent courses of a few days' duration. If the drug is prescribed in an adequate quantity, the intelligent patient will soon learn to regulate his own dose. He should be instructed to take it regularly, day by day, until the first appearance of headache or anorexia, the drug is then stopped for two days and a further course begun. It is no solution of the problem to attempt to offer to the more fastidious patient some refined preparation of digitalis or an

allied body, in the hope that gastric disturbance will be thereby avoided. On the contrary, the patient is to be congratulated when he has determined for himself the quantity of the drug

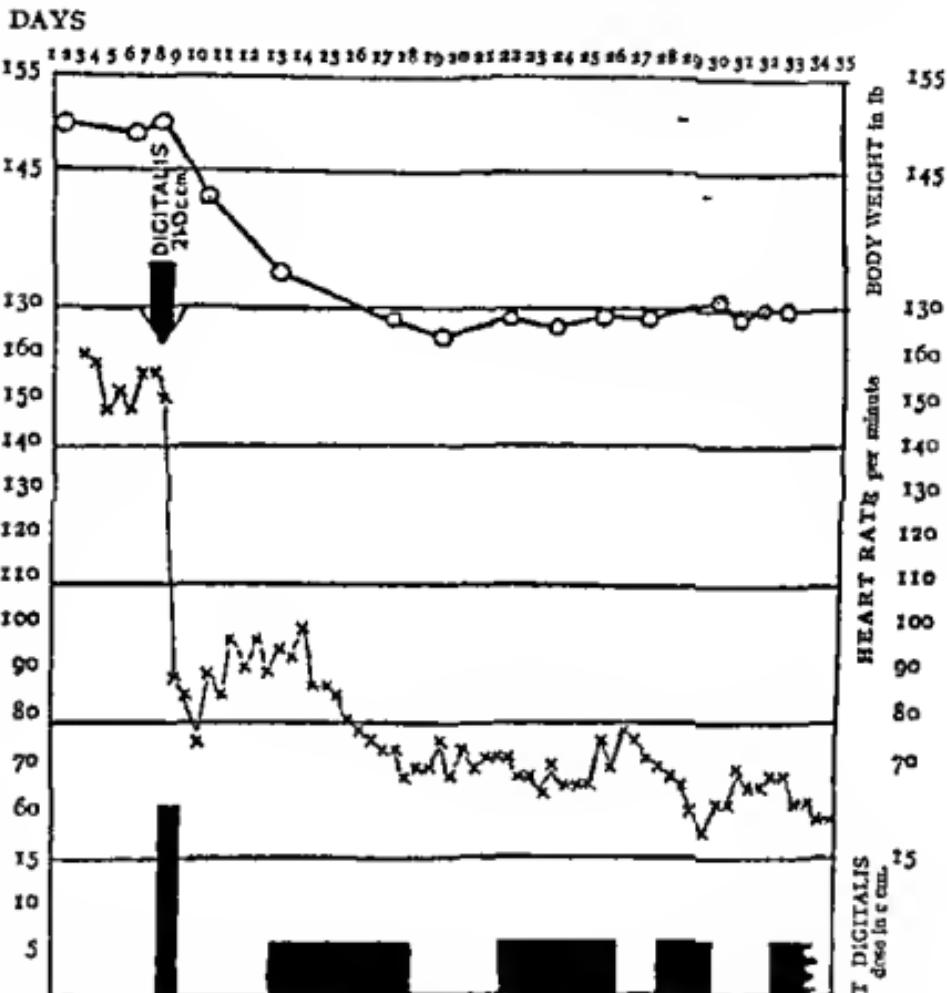


FIG. 3.—To show the effect of massive doses (21 c.c.m. of digitalis tincture in divided quantities) in a woman aged 48, suffering from rheumatic heart disease, congestive failure, and auricular fibrillation. The ventricular rate was 155 before the drug was started. Two days later the rate was 76. No intoxication was induced. Subsequently, maintenance courses of 30 minims thrice daily were employed until nausea was induced

which he is capable of taking over a short period of time and which is associated with headache and dyspeptic symptoms. Intoxication of this nature is a certain indication that active principles are in use. By stopping the drug for two days,

unpleasant symptoms rapidly subside. A preparation said to be devoid of "irritant" properties is almost certainly inert, so far as any desired action on the heart is concerned.

Pills or friable tablets of the powdered leaf, each $1\frac{1}{2}$ grains, provide a convenient method of regulating maintenance dosage, particularly in the ambulant patient, but in hospital practice the nurse can readily measure the dose in minims in a medicine glass at the bedside. It is never good practice to order digitalis in a drop bottle. The size of a drop varies enormously, and seldom corresponds in volume to 1 minim. When the pure tincture is in use, it is preferable to order an easily measured quantity—such as 60 minims daily—rather than suffer the vagueness of 20 or more drops three times a day. Inexact digitalis dosage is fraught with danger to the patient and confuses the practitioner in his management of the drug therapy. The tincture is said to deteriorate on keeping in a watery solution, but its prescription in a mixture made up to strength of 10 minims to the dose is certainly preferable to misguided attempts to gauge the dosage by a count of the fall of drops from a bottle. In arranging the dose, it is useful to remember that $1\frac{1}{2}$ grains or 0.1 gm of the leaf, and 15 minims or 1.0 c.c.m of the tincture, are all of approximately equal potency.

The first maintenance course of digitalis is begun on the third day after the digitalizing quantity has been determined—that is to say, three days after the first appearance of minor symptoms of intoxication. It cannot be too strongly emphasized that the exact quantity of digitalis required as a maintenance dose can only be determined by the method of trial and error, it varies considerably for different individuals, apparently being influenced to some extent by body-weight, just as is the digitalizing dose.

Whether the course of digitalis should be short or long depends largely on the quantity taken, and on the interval between successive courses. An easily remembered rule is to omit all medications on Saturdays and Sundays, this implies a short course of digitalis therapy of five days' duration. Some people seem to do better on this shorter course than on a longer

one of ten to fourteen days, before an intermission is necessitated by the appearance of headache or nausea. Furthermore, the omission of two days regularly in each week is a system which lends itself to ready cooperation. Each individual must learn to discover the method best suited to himself.

A start may be made by ordering 15 minimis of the tincture, three times a day (or three 1½-grain pills), to be taken regularly and discontinued on the first sign of intoxication. The patient is instructed to note the number of days which elapse between the start of the medicine and its discontinuation. If the course amounts to more than a week, then the quantity of the drug taken daily may be increased by a dose of 10 or 15 minimis in the second course, which will therefore tend to be shorter than the previous one. In this way it is usually possible so to adapt the doses that the drug is taken for five consecutive days—two days being omitted at the conclusion of each course. For similar reasons, should intoxication be induced in the first course, after perhaps only three or four days' medication, then in a subsequent course a reduction of 10 or 15 minimis in the daily dose will help to determine the quantity which the individual can tolerate for five days, with a two-day interval between successive courses.

The patient should be encouraged to take as much of the drug as his tissues will tolerate. The simple rule of controlling the dose according to symptoms is much more effective than purely arbitrary rules regarding the rate of the pulse. The intelligent patient will ultimately learn to regulate his own dosage by his sense of well being, and this is certainly a better guide than is to be found in spasmodyic counts of the pulse rate. There is no more important aspect of digitalis therapy—and none more often neglected—than the efficient regulation of maintenance dosage. Quite briefly, it is better to rely on symptoms than on the heart rate.

THE INDICATIONS FOR DIGITALIS THERAPY

It is only in particular circumstances that real benefit follows the use of digitalis. When symptoms of myocardial insufficiency exist and are made manifest by obvious dyspnoea,

dependent oedema, increased venous pressure and congestion of the hepatic, pulmonary or peripheral circulation, then digitalis is likely to be helpful. Its use in the absence of such symptoms finds little or no support in clinical experience. Everyone will agree that congestive heart failure is the all-important indication for the use of digitalis.

It is less commonly realized that the rate of the pulse is of little or no consequence in forming an opinion as to whether digitalis is indicated or not. Tachycardia is often of reflex or nervous origin and, occurring during the course of active tuberculosis, septicæmia, pneumonia, thyrotoxicosis, or in anxiety states, it is often a measure of the degree of toxæmia or of the emotional disturbance. Digitalis is not indicated merely because a heart is rapid. It is illogical to attempt to interfere with a heart adjusted to the body's immediate requirements. On the other hand, if congestive failure is present or appears imminent, then digitalis is likely to be of benefit.

Digitalis is also indicated in that form of cardiac distress spoken of as left ventricular failure, in which dyspnoea predominates and in which peripheral oedema is minimal. It is in these patients that its powers of prevention of further incapacity are often so remarkable. Minor degrees of dyspnoea—particularly in sufferers from hypertension—are often eased by suitable maintenance dosage. Rapid and complete digitalization is of particular benefit in the paroxysmal arrhythmias, but it has apparently little power to prevent further attacks. When the origin of a peripheral oedema is obscure, digitalis in adequate doses may be employed as a therapeutic test. Finally, careful digitalization is of the utmost value in the stage preceding the use of quinidine.

These indications for the use of digitalis are well established. In such conditions the drug may be expected to produce results of value. It is however, still common to find it prescribed in various states in which it can be of no real benefit, and in which increasing evidence points to a deleterious effect on the circulation as a whole. It should be realized that harm may result from its inappropriate use. The routine use of digitalis increases the mortality in lobar pneumonia, is believed

to increase the post-operative death rate in thyrotoxicosis, and handicaps recovery in the peripheral circulatory failure of shock and collapse

DIGITALIS INTOXICATION

The method of controlled digitalis therapy outlined above depends largely for its successful use on a careful study of the patient's symptoms—minor degrees of intoxication frequently preceding the release from circulatory distress. It is fortunate that the symptoms of digitalis poisoning occur in a definite sequence. Beginning with frontal headache and anorexia, and passing on to nausea and vomiting, they are easily recognized by the patient, who has thus an early certain indication to discontinue the further use of the drug until such time as the practitioner feels he may begin its re-administration. Diarrhoea, yellow and green vision and, in elderly men, muttering delirium and minor hallucinations—often taking the form of rectangular figures—are less frequent symptoms of digitalis poisoning. They disappear when the drug is discontinued for a few days. It is true that a heart rate below 50, the appearance of multiple extrasystoles, especially coupling of the beat, or the appearance of heart block, either partial or complete, are all danger signals. These arrhythmias are likely to precede the general symptoms of intoxication in elderly people, far advanced in congestive heart failure, irresponsive to the usual doses of the drug. When recognized the dose should be discontinued for at least three days, or until such time as the arrhythmia subsides. The complete heart block of digitalis is a rare condition, and when it does occur, seldom gives rise to any distress. More common and more dangerous is the development of a paroxysmal tachycardia of ventricular origin. This may pass undetected unless a careful watch is kept on the rate of the heart, as it is frequently accompanied by a pronounced pulse deficit. The symptoms depend chiefly on its duration, the degree of heart failure tending to advance, but the rhythm itself may be responsible for a state of mental confusion, delirium, epileptiform attacks, or sudden death.

DIFFICULTIES IN THE ADMINISTRATION OF DIGITALIS

It is quite exceptional to meet with a patient in real need of digitalis who is intolerant on account of an idiosyncrasy to the drug. An ineffective control of maintenance doses is the common explanation of an alleged gastric idiosyncrasy. If digitalis is required in such circumstances, and the patient is equally intolerant to digoxin tablets (each 0.25 mgm equivalent to 15 minims of the tincture) or digitaline granules (1/240 grain or 20 minims tincture), then resort must be made to the rectal or intravenous routes. Portal congestion with an engorged gastric mucosa is often a source of dyspepsia. Repeated bouts of vomiting and retching may then preclude effective oral administration. With the lower bowel empty, 60 to 120 minims of the tincture may be added to 2 or 3 ounces of warm 5 per cent glucose saline, and injected slowly, daily. Advantage can be taken of this route for a few days before resuming oral administration, if the symptoms of congestive failure are not really urgent. The intravenous route can be employed with great certainty. On account of the prompt response to such a valuable preparation as digoxin, the dose should not exceed 1.0 mgm. It is available in convenient ampoules each containing 0.5 mgm in 1.0 c cm of 70 per cent alcohol. On this account, it is best diluted ten times with sterile water or saline immediately before intravenous injection. When an unknown amount of digitalis has been previously administered, and some partly expelled by the vomiting of portal congestion, the intravenous dose should not exceed 0.5 mgm. This quantity may be repeated in six or eight hours, if symptoms continue urgent. Oral dosage is, with few exceptions, the method of choice, on account of its safety, but advantage can also be taken of the potency of intravenous digoxin in such emergencies as the paroxysmal nocturnal dyspnoea and acute pulmonary oedema of left ventricular failure.

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CHAPTER III

DRUGS AFFECTING THE CONTROL OF THE VASOMOTOR SYSTEM

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CHAPTER III

DRUGS AFFECTING THE CONTROL OF THE VASOMOTOR SYSTEM

"A man's life is the gift of his arteries, just as Egypt is a gift of the Nile," wrote Sir William Osler many years ago, and even if he could rewrite it to-day he would find difficulty in improving his statement. Perhaps he might substitute arterioles, and it is possible that he might like to add "and his endurance is the result of his vasomotor adaptability."

Those trained athletes, the Finns have shown what mental and physical fitness can effect and endure, and have provided interesting illustrations of their prowess. A recent picture showed some of them basking naked in the snow, looking as if they enjoyed it, and the subjoined text told that they did this after a hot bath as a kind of training exercise, that it kept them fit and helped them to resist both fatigue and cold. The trained athlete automatically adjusts his vasomotor mechanism to adapt the blood supply of different parts of his body to varying needs, and these automatic adjustments are both rapid and efficient. Such a trained man can accommodate himself to variations of temperature much more readily than the unfit. In the cold, his skin vessels close, and he retains heat better, and his muscles by their greater activity provide heat internally; in the heat, his cutaneous vessels relax, he sweats easily and loses heat more rapidly. Fitness and training depend on these adjustments, so that the trained man endures that which the unfit merely suffers, and physiological facts suggest that special kinds of training may be particularly useful in increasing vasomotor adaptability.

The most general vasodilatation which can be obtained in man is that which follows immersion in a very hot bath. Here the skin vessels are fully dilated and the central vessels also relax, so that a marked fall in blood pressure results. Faintness

is not uncommon in the bather who stands up quickly, and in unfitness or disease serious results may ensue, for acute pulmonary oedema and even coronary occlusion sometimes follow such a bath. This is well known, and those who seem likely to suffer are advised to avoid the hottest rooms at the Russian or Turkish baths. After such baths comes a cold douche which produces a peripheral vasoconstriction, a rise of blood pressure, and a sense of warmth and well-being which may last for hours. Provided that neither the heat nor the cold is too prolonged, the experience is invigorating, and the application of the cold shower, douche, or snow does not produce any discomfort or shock. It is possible that some such therapeutic knowledge was the real basis of the Roman fondness for hot baths. It is known that they possessed no effectual soap and depended on sweating and scraping for cleansing the skin, but it is difficult to believe that cleanliness was the motive behind the Roman bath. It was the Greek who taught the Roman the bathing habit, the Greek, to whom physical fitness was a religion, and training a cult which long experience had brought to a high degree of perfection. and the evidence at our disposal seems to suggest that the use of hydrotherapy in Roman cities was part of a general athletic training. Those who through natural indolence, age or over-feeding were losing the lines and vigour of youth, and that vasomotor agility which went with youth and fitness, found such baths helpful—just as the same kind of people to-day resort to our Turkish baths.

DISORDERED VASOMOTOR CONTROL

There are a number of diseases in which vasomotor control is upset, fevers, such as pneumonia or typhoid, produce a hot dry skin, whereas in influenza, acute rheumatism, and abortus fever the skin is typically moist. This occurs because certain toxins produce fever and vasoconstriction by central stimulation although in larger doses they produce paralysis of the centre, with that cold damp, clammy skin, peripheral circulatory failure, and cyanosis which almost always betoken a fatal issue. Stimulation of the sympathetic system causes general peripheral constriction with some central relaxation. The

skin turns pale, and the heart, lungs, and brain receive a more generous blood supply. On the other hand, stimulation of the parasympathetic results in a general relaxation of blood vessels. The centres for both these systems lie in the medulla. It is possible that there are other control centres for blood vessels, some in the spinal cord itself, which can regulate vascular tone, but it is improbable that these centres, if they exist in man, are of great importance. Carbon dioxide is the outstanding stimulant of the vasomotor as well as of the respiratory centre, and reduction of carbon dioxide in the blood through its action on this centre causes relaxation of arterioles and even capillary dilatation.

Many toxins which produce fever also cause vascular relaxation, both in arterioles and capillaries alike, so that fever is now used to differentiate between vascular spasm and arterial narrowing due to disease. When cold dead feet, resulting from vascular spasm, become warm after an injection of T A B vaccine, the condition will probably react favourably to sympathectomy, whereas those feet which do not become warm, even when the patient shows marked fever, will not be helped by operation, since vascular disease and not spasm is the causal factor. This relaxation of blood vessels in fever is important in other respects. It can be utilized to produce tissue reactions in special forms of treatment, and is probably the basis of improvement produced by artificial fever in syphilitic disease of the brain. At present there is no certain knowledge of the causes of capillary tone and, although pituitary and adrenal secretions have each been considered the controlling factor, conclusive evidence is lacking. It is not even known whether or not the capillary bed is normally regulated by sympathetic nerves.

Fainting is a common and particularly interesting event. It is characterized by pallor, a profound fall of blood pressure with a small volume pulse, marked bradycardia and frequently loss of consciousness. Sweating usually occurs. Neither the vagus nor the sympathetic acting alone can produce such effects and, although clinicians call such faints vasovagal attacks, physiologists suggest that sympathetic inhibition is a

more probable cause than vagal stimulation. In the treatment of fainting, alcohol and all the so called stimulants have been used, but the one really effective drug is atropine, which acts by depressing the vagus.

There are important local vasomotor mechanisms quite apart from and independent of the centres. The simplest way of increasing the blood supply to a muscle is by working that muscle; and the peculiar cramp which appears when a muscle is worked without a corresponding blood supply is as well known as it is painful. Intermittent claudication is due to this failure of supply, and the phenomenon is familiar to those who apply puttees too tightly and then attempt to march. Massage acts in a similar manner to exercise, and temporarily and locally increases muscular blood supply, but it cannot take the place of exercise if muscles are to be maintained in an optimal condition. Stimulation of the anterior horn of the segment which supplies a muscle also produces vasodilatation in the muscle.

THE CORONARY VESSELS

The coronary blood flow is particularly important and interesting, defects in the supply are common and produce serious results. The physiology of the cardiac blood supply is peculiar. In systole, the heart muscle by its contraction tends to empty the cardiac blood vessels, the main coronary blood flow taking place in diastole, depending upon diastolic blood-pressure. Increases in systolic force or duration will tend to lessen the blood supply, and an increase in the heart frequency, by lessening the duration of diastole, also reduces the supply. Curiously enough, in auricular fibrillation although the heart rate is increased, the coronary flow remains relatively good, a condition which is the probable explanation of the rare association of angina and auricular fibrillation.

Oxygen lack carbon dioxide excess and the accumulation of the metabolites, which result from muscular activity, all produce coronary relaxation. Amyl nitrate, by a direct action on the smooth muscle of the vessel walls, causes a considerable coronary dilatation, and certain metabolites, and especially purine derivatives, such as caffeine and theophylline, are even

more powerful in increasing coronary blood flow. The nervous control of the cardiac blood vessels varies in different animals and has not yet been determined with certainty in man, but it is certain that the coronary arteries are generously supplied with nervous connexions and that the vasoconstrictor fibres travel in the vagus, although possibly they may be of sympathetic origin.

The frequent appearance of nervous factors in angina suggests that control of the cardiac blood vessels must be reasonably adequate, but this control is complex, and it is very difficult to determine the effect of drugs acting via the autonomic nervous system. Sympathetic stimulation in animals usually produces coronary relaxation, more marked if the vagi are paralysed by atropine, but the effect of a dose of adrenaline is variable and, in man at any rate, its action seems to depend more upon local conditions than on its effect on the vasomotor centre.

DRUGS IN ANGINA PECTORIS

Although the etiology of angina is not yet completely worked out, it is certainly due to an ischaemia of the myocardium relative to the work done. Coronary spasm could produce anginal symptoms without any increase in work. Failure of coronary relaxation under increased work or even an uneconomical acceleration of the heart might equally produce pain. Drugs which effect a vascular relaxation by dilating the coronary system ought to relieve anginal pain by improving the blood supply. It will be noted that such remedies can be effective only if the coronary vessels are capable of dilatation, but from what has been said above about the peculiarities of the coronary flow, namely that increased heart rate and a low diastolic blood-pressure tend to diminish coronary supply, it would seem probable that the effect of vasodilators is in relieving pressure and the lessening of the cardiac work. It is certain that in cases of coronary occlusion such vasodilators are not only ineffective but, by increasing the heart rate and tending to lower peripheral blood-pressure, are dangerous. The important points in the treatment of coronary occlusion are to induce such a state of mental and physical

quiescence as will reduce cardiac work to the lowest level, to relieve pain, which is certain to produce restlessness and may favour vascular spasm, and to maintain the nutrition of the damaged heart-muscle as far as possible. For the pain, morphine is almost essential, and the administration of oxygen is often useful in maintaining cardiac nutrition. An oxygen tent is perhaps the most comfortable method, but the new B.L.B. nasal apparatus is at least as effective, and is far cheaper to use and easier to manage. A short trial will generally suffice to convince the nervous patient of the help oxygen affords, and he will cooperate and become quite unwilling to relinquish the apparatus. The nitrites relax all smooth muscle, but the arterioles, being the most sensitive, are affected chiefly. Amyl nitrite, when inhaled, enters the blood stream via the alveoli, and circulates rapidly. Its action is immediate and marked but is brief, eight minutes at most. A considerable fall of blood pressure may produce a curious feeling of instability, and a headache lasting some hours may follow, although many patients with anginal symptoms obtain great and immediate relief from its use. If amyl nitrite is the drug selected the capsule must be carried so that it is immediately available, pinned beneath the lapel of the coat, or in the pocket of the pyjama jacket, and once a capsule has been expended, it must be replaced immediately. As a general rule the smaller capsules are better than the larger ones, and tolerance to the inhalation is not established (2-minim, 3 minim, and 5-minim capsules are obtainable). Many other nitrites and organic nitrates have a similar action but, being less volatile, are less rapid in action and last longer without causing so great a fall in blood pressure. One of the best is glyceryl trinitrate, in a tabella of a chocolate base containing $1/120$ of a grain or in a 1 per cent solution. The tabella is chewed, as the nitrate is more readily absorbed by the mucosa of the mouth than from the stomach.

The anginal subject so ordering his life that he avoids exertions or emotions which may evoke his pain, controlling his meals and his temper may, with the occasional use of a tabella before an unavoidable business meeting or a walk which is likely to try him, secure a maximal freedom from discomfort,

and a long and useful life. The mode of living is the important factor. The drug should be used to assist the attainment of an ideal, not to change the mode of life. The other nitrates are generally less useful. They are sodium nitrite in doses of $\frac{1}{2}$ to 2 grains in solution, erythrol tetranitrate, which has a prolonged effect, and mannitol hexanitrate, which produces even more lasting, though less marked, relaxation. All the xanthine derivatives relax the coronary and renal arteries, and produce a diuresis and relief from anginal pains. They may be used alternately in order to prevent addiction to any one of the series. Sometimes a marked preference for one preparation appears, and it may be useful to continue to give this, although as a rule a periodic change is advisable.

OTHER DRUGS

Theobromine and its derivatives relax both coronary and renal arteries, theobromine and sodium salicylate (diuretin) is particularly effective, but since it is easily decomposed when in solution, it must be given in tablet form and is most useful in large doses. The pharmacopœial dose is 10 to 20 grains, but the best results will only be secured by doses of at least 30 grains three times a day. Unfortunately, this dose sometimes produces digestive disturbance.

Theobromine and *sodium acetate* (agurin), in doses of 15 grains thrice daily, sometimes proves more helpful than the salicylate salt. Unfortunately, the acetate is more hygroscopic than the salicylate so, although both tend to decompose in solution, the acetate cannot be kept in powdered form for long.

Theophylline is even more diuretic and rather more likely to upset the stomach than the foregoing salts, and has the further disadvantage of producing definite excitement in susceptible people. The average dose is from 1 to $2\frac{1}{2}$ grains thrice daily.

Euphyllin, $1\frac{1}{2}$ to 3 grains by mouth or in larger doses by injection or per rectum, has a similar action.

It has been claimed that one or the other of these substances will infallibly relieve cardiac pain—even the pain of coronary occlusion. Needless to say, this statement is untrue.

DRUGS PRODUCING VASOCONSTRICTION

Vasoconstriction is relatively seldom required, it may be useful in allergic reactions and may be produced by the injection of adrenaline in doses of 5 to 20 minims of 1 in 1,000. This is best given in repeated small subcutaneous doses, and must never be administered intravenously. Local vasoconstriction in operation fields can be secured by the addition of adrenaline solution to the local anaesthetic. This is especially necessary when the local anaesthetic favours vasorelaxation or fails to produce a vasoconstriction, or when the operation site is particularly vascular.

Adrenaline solution injected subcutaneously, or ephedrine given by mouth or hypodermic injection, does produce some degree of vasoconstriction, a rise of blood pressure and relaxation of bronchioles, but it is for their action on the bronchial muscle or on the excitability of the myocardium that these drugs are commonly administered. They have been given in circulatory collapse and in enuresis.

Benzedrine, recently introduced as a popular "tonic," causes a marked rise in blood pressure from a general increase in vascular tone, but its useful effects are not directly associated with the raised blood pressure.

Ergotamine tartrate, 1/60 to 1/20 grain, by mouth, is sometimes remarkably effective in relieving migraine. It produces a definite vasoconstriction with a rise of blood pressure, although it is not at present known how it affects the relief of the migraine syndrome.

On the whole then, control of vasomotor mechanism is partial and temporary only, and perhaps it is a good thing that this is so, for prolonged vasodilatation and the profound fall of blood pressure associated with it would be as disastrous as an enduring spasm and the ensuing hyperpiesia.

CHAPTER IV

EXPECTORANTS AND LINCTUSES

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CHAPTER IV

EXPECTORANTS AND LINCTUSES

CATARRHAL and other inflammatory conditions of the respiratory passages are almost without question the commonest of all affections in these islands. Cough and expectoration are often annoying, distressing, and even alarming symptoms for which patients demand help and expect relief. The judicious use of expectorants and linctuses can be of great assistance, and it is probable that the "bottle of medicine," in spite of the derision of the scientific therapist, will long remain in favour, both with patients and practitioners, in the form of the cough mixture. Even when specific bacterial or chemotherapeutic measures are available, the relief of symptoms may contribute notably to recovery as well as to the patient's comfort.

There is an aphorism of Forchheimer which is often quoted, although I have not been able to trace its original form, to the effect that expectorants are often disappointing and uncertain, but that he would be very sorry to be without them. Probably most practitioners would endorse this view, which is an expression of belief in the usefulness of this class of medicaments, but a confession of incomplete knowledge of their modes of action. It may therefore be of some interest to study how far experience and pharmacological investigations have elucidated these problems.

J A Gunn (1927) has given an interesting description of the protective mechanisms of the respiratory passages. He points out that the action of the cilia of the epithelium of the trachea and bronchi is stronger and more effective than is usually recognized, its propulsive rate being about one inch a minute, and that this, combined with the normal secretion of the bronchial mucous glands, is sufficient to keep the air passages clear in health. He thinks that the bronchial muscle may also assist by a peristaltic action, although this was doubted by A J Clark.

(1937), who suggested that a massaging effect may be produced by the respiratory movements on the bronchi, since it is known that they become longer and wider with inspiration, and shorter and narrower with expiration. This may well have a milking effect on the bronchial mucus. It is interesting to note that stimulation of the central end of the superior laryngeal nerves causes reflex swallowing as well as cough. It is therefore probable that in health the bronchial mucous secretions are swallowed.

THE CAUSE OF THE COUGH

Cough is a sensitive reserve mechanism to deal with any abnormal increase of fluid in the air passages and with foreign bodies. It is one of the most important protective reflexes, and fortunately it is one of the most easily evoked. Its important function in safeguarding the respiratory passages is easily recognized when we consider the dangerous conditions which ensue when the cough reflex is damaged or abolished by disease, or abolished by anaesthesia. The air passages become unable to expel accumulating secretions or inflammatory products, and are left open to the inhalation of foreign material from the pharynx or from outside the body. The afferent paths by which this reflex may be started are extraordinarily widespread. The most direct and important are the sensory nerves of the pharynx, the larynx and bronchi, namely the glosso-pharyngeal nerve to the pharynx and the vagus to the larynx and bronchi, its superior laryngeal branches being especially effective. The visceral branches of the vagus supplying the abdominal viscera, notably those to the stomach may also excite cough as may also strong stimulation of the skin, and of nerves such as the auricular branch of the vagus.

The cough centre is presumed to be in the medulla, and to be situated near those controlling respiration and vomiting. Certain features of the cough reflex are of interest, especially in relation to its treatment. The immediate closure of the glottis, which precedes the forcible expiratory effort, serves the double purpose of preventing the inhalation of foreign material and allowing the development of the increased pressure in

the air passages, which is the main factor in the expulsive action of cough

Another feature of interest is the difference in the response to irritation of the various parts of the air passages. Sneezing is the reaction in the nasal passages. If the pharynx is the site of the exciting stimulus, a harsh 'hawking' cough results, sometimes with retching or even vomiting. The larynx when irritated gives rise to a violent noisy cough, frequently repeated. The trachea and main bronchi are only slightly less sensitive, and the cough induced by irritation, inflammation, or by an inhaled foreign body is very similar but slightly less urgent, unless the material or foreign body is projected against the under surface of the vocal cords, when it may become alarming. The sensitiveness of the bronchial mucous membrane gets progressively less as the bronchi gets smaller, and it is remarkable that the infundibula and the alveoli areas that it would seem essential to keep free and patent are not cough-provoking, whereas on the other hand irritation of the pleura is often distressingly effective.

The effects of an inflammatory infection of a mucous membrane are familiar in the symptoms of coryza or nasal catarrh—the irritating and distressing dry stage, when the ducts of the mucous glands are partially occluded by the inflammatory exudate into the submucous tissues, next, the excessive secretory activity of the mucous glands with the copious discharge of mucus, and then resolution with recovery—or the formation of pus and the discharge of muco-pus. Similar conditions, with the substitution of cough for sneezing, occur in the larynx, trachea, and bronchi, when they become the sites of infection. The dry stage is associated with a troublesome ineffective cough which causes painful retrosternal soreness, the exudative stage with copious mucoid expectoration, usually becoming muco-purulent before recovery occurs.

EXAMINATION OF SPUTUM

The investigation of expectoration, microscopically and bacteriologically, is now almost a routine procedure in all respiratory diseases. The observation of the physical characters of

sputum is often neglected, and yet it may give most valuable information in regard to diagnosis, and be particularly helpful in suggesting the use of expectorants or sedatives. Most sputum cups are made of porcelain or enamelled metal, and in consequence only the surface layer of the sputum can be seen. I generally ask for the sputum to be emptied into water in a glass vessel, preferably of conical shape. It may be so viscid or tenacious that it is difficult to remove from the cup, which gives a suggestion for the use of expectorants to make it thinner and therefore more easy to expectorate. In pneumonia the sputum is very sticky, and the difficulty in expectorating it into the sputum cup or paper handkerchief often distresses and exhausts the patient. Copious frothy mucoid or muco-purulent sputum generally floats and suggests of bronchial irritation or inflammation, whereas sputum in which pus predominates is more often nummular and the pellets may remain discrete, pointing to disease of the lung parenchyma, such as tuberculosis. The three layers of bronchiectatic sputum are well known and generally recognized. In sputum from a pulmonary abscess, or from an empyema which has opened into a bronchus, the pus settles rapidly to a uniform layer at the bottom, with the mucoid or muco-purulent aerated exudate from the bronchi forming a floating scum on the surface.

THE BASIS OF TREATMENT

Having determined the cause of the cough and the character of the expectoration it is important to decide the appropriate treatment of each. In regard to cough, it may be necessary to promote it and to increase its effectiveness or, on the other hand, in cases in which it is useless and exhausting, to allay or suppress it. The character of expectoration can be altered by rendering it more watery, less tenacious and sticky or, conversely, when it is copious watery, or excessive, attempts may be made to lessen its quantity or modify its character. It is in the achievement of these objects that expectorants, antispasmodics, respiratory stimulants, and sedatives (both general and local) can be usefully employed.

EXPECTORANTS may be defined as drugs which promote

the expulsion of secretion or exudates from the respiratory passages, or which modify their characters. They were formerly classified into stimulating and depressing groups, the former being supposed to increase blood pressure and diminish secretion, the latter to lower blood pressure, increase secretion, and promote expulsion. These terms are now generally discarded, and no hard and fast pharmacological differentiation is at present practicable. The most useful classification is that of the late Prof. W. E. Dixon (1936), which slightly modified is as follows—

(1) *Demulcents*—which are soothing to the mucous membrane of the pharynx and oesophagus, and may possibly promote secretion. Examples are liquorice, gum acacia, gum tragacanth, and glycerin. Various tisanes and hot drinks may be useful in the same way.

(2) *Nauseants*—Most emetics given in sub-emetic doses act as expectorants. The most commonly used are ipecacuanha emetine, tartar emetic apomorphine, and the salts of ammonium especially the chloride and carbonate. The drugs acting through the saponins, including squill, senega, quallia, and grindelia may be included. Nauseants probably act through the gastric branches of the vagus, producing by reflex action an increase of secretion from the mucous glands of the bronchi. There is some pharmacological evidence that certain members of this group—ipecacuanha, tartar emetic, and grindelia—may also stimulate the central mechanisms for bronchial secretion and cough.

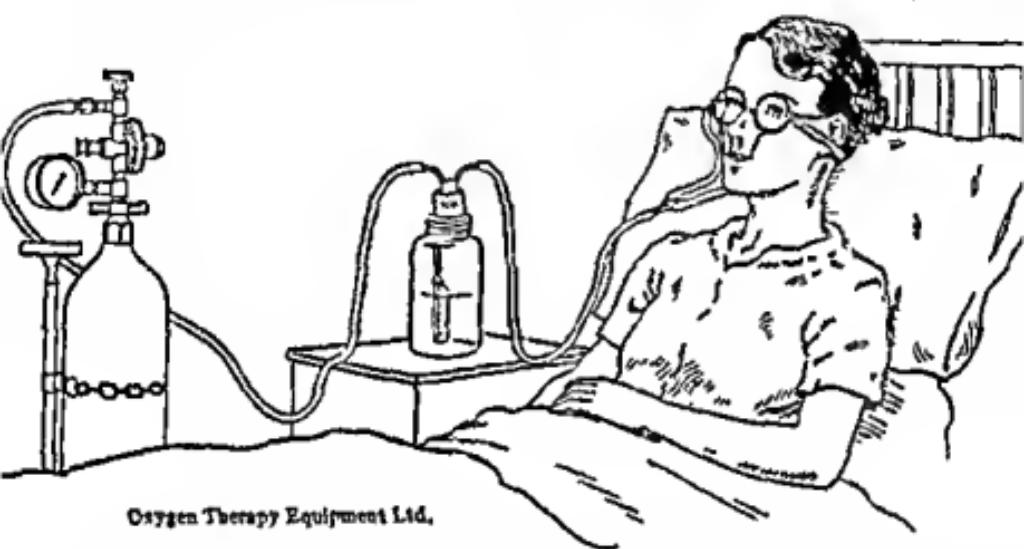
(3) *Saline expectorants*—sodium and potassium salts, especially the bicarbonates and chlorides and to a less extent the citrates and acetates. The ammonium salts in small doses are also often included in this group. The mode of action is not yet certain. It is supposed to be at any rate partly by salt action. Iodide of potassium is probably the most important member. It is generally believed to increase secretion from the mucous glands by direct action through the blood and lymph.

(4) *Aromatic or antiseptic expectorants*, such as the volatile oils, the balsams of tolu and Peru, creosote, guaiacol, tar, terebene and terpene hydrate. They were employed on the supposition that they were excreted by the mucous glands, but it is more than doubtful if they reach the bronchi in sufficient concentration to exert any effective antiseptic action. They are still extensively used, especially in association with other drugs and are present in some well known proprietary preparations.

BRONCHO-DILATOR OR ANTISPASMODIC AGENTS

—Although it is doubtful whether or not the bronchial muscula-

ture exerts any definite effect in promoting expulsion of mucus or other exudates from the bronchi, it is certain that when it is over-active, as in asthma and other conditions of bronchial spasm, it renders expectoration more difficult and may aggravate cough. The use of antispasmodic drugs may therefore be a valuable adjuvant to expectorant mixtures, of these the most important are the atropine group, comprising belladonna, stramonium, lobelia, and hyoscyamus. These act by depressing the vagal motor nerve-endings and are therefore cholinergic. Adrenaline and ephedrine act by stimulating the



Oxygen Therapy Equipment Ltd.

FIG 4 *

sympathetic inhibitory or dilator fibres, and are adrenergic. Other drugs having a dilator effect are nicotine, in certain stages of its action when it depresses the vagal ganglia, and nitrates and papaverine which act directly on the muscle.

OTHER MEASURES PROMOTING EXPECTORATION—When, owing to increasing cyanosis and anoxæmia, patients become drowsy or restless, and unable or unwilling to cough, active measures are urgently needed. Strychnine hydrochloride or sulphate given hypodermically in doses of $1/30$ grain (and repeated at four- to six-hour intervals short of producing

* Blocks for figures 4 and 5 kindly lent by Messrs A. Charles King Ltd, 33 Devonshire Street, W 1, from whom the apparatus can be obtained

actual twitching) may be helpful by stimulating the respiratory and cough centres and increasing reflex activity. Coramine, cardiazol, or their equivalents and substitutes (anacardone, nicamide, cardatone, dacorene) may be helpful, especially when given subcutaneously. Large doses of ammonium carbonate up to 10 or 20 grains given in milk may help to start expulsive efforts. In infants and young children emetic doses of tincture of ipecacuanha are often used. Stimulation of the skin of the chest and back by strong liniments, poultices, or other



FIG. 5.

methods of heat application, such as antiphlogistine or diathermy, may also promote expectoration.

In severe cases the administration of oxygen is of the greatest value; it is now almost a routine procedure in cases of grave respiratory disease in which it may be an important aid in promoting expectoration. When possible it should be given continuously and the amount regulated by means of a flow-meter. The nasal route is a most convenient method, especially when the ingenious Tudor Edwards' (1938) spectacle-frame nasal catheter carrier is employed (fig. 4).

A highly efficient mask has recently been introduced in America by Boothby, Lovelace, and Bulbulian (1938) and is now available in this country as the " B L B inhalation apparatus " (fig 5) By varying certain adjustments, it is claimed that an alveolar concentration of more than 40 per cent. oxygen can be maintained with a flow of three litres a minute, and with a flow of four litres a concentration of 55 to 60 per cent , and with six or eight litres as much as 90 to 95 per cent may be reached in the alveoli This apparatus will doubtless prove to be a valuable addition to our methods of oxygen administration, but to many patients a mask gives at first a feeling of suffocation, and some are unwilling to persist in its use, especially when it is retained in position by a band round the head

Oxygen tents are now well known in this country, largely owing to the pioneer work of the late Dr E P Poulton They may be life-saving in infants, extremely ill patients, and after severe lung operations It should be remembered that carbon dioxide is a powerful stimulant of the respiratory centre and that inhalation of oxygen with a 7 per cent admixture of carbon dioxide for short periods may stimulate deeper breathing and expectoration

EXPECTORANT MIXTURES

In prescribing expectorant medicines it is important to bear in mind what the preparations ordered are intended to effect It may be necessary to use several different drugs and, in consequence of this, cough mixtures are often criticized and even derided as ' shot gun " or " blunderbuss " in character They may even include preparations with actions to some degree antagonistic or in opposition, and yet be effective, even though theoretically inconsistent The experienced practitioner looks to the pharmacologist for explanations of the effects of his drugs, but he is not prepared to accept condemnation on theoretical grounds of mixtures which his experience has shown to be helpful

In the dry stage of a catarrhal infection of the respiratory passages, warm or hot demulcent drinks, tisanes, or lozenges

may be useful. A saline diaphoretic mixture is often prescribed such as

R.	Liquoris ammonii acetatis diluti	-	-	120 minimis
	Potassii citratus	-	-	-
	Tincturæ ipecacuanhæ	-	-	15 minimis
	Aquam chloroformi ad	-	-	1 ounce

Every six hours

Vinum antimoniale, B P 1914-15, to 10 minimis may be substituted for the tincture of ipecacuanha, or small sub-emetic doses of apomorphine hydrochloride. Formerly one minum doses of tincture of aconite were frequently included in such mixtures. All of these come under the category of "good remedies out of fashion."

A sedative or soporific powder or mixture at night is often valuable, even in mild cases, and Dover's powder, now called *Pulvis ipecacuanhæ et opii, 10 grains*, is most popular for this purpose. If the cough is dry, painful, and ineffective, the well-known Brompton Hospital "hot-water" mixture is useful —

R.	Sodi bicarbonatis	-	-	-	15-20 grains
	Sodii chloridi	-	-	-	5 grains
	Spiritus chloroformi	-	-	-	5 minimis
	Aquam anethi destillatam ad	-	-	-	1 ounce

This is given with an equal quantity of hot water. It may be repeated several times in the day.

In the exudative stage of catarrhal affections of the respiratory passages various mixtures of saline and nauseant expectorants are generally employed, e.g.

R.	Tincturæ scillæ	-	-	-	-	20 minimis
	Tincturæ ipecacuanhæ	-	-	-	-	10-20 minimis
	Potassii citratus	-	-	-	-	10 grains
	Syrupi tolutani	-	-	-	-	30 minimis
	Aquam chloroformi ad	-	-	-	-	1 ounce

Three times a day or six hourly

Tinctura opii camphorata, 10 to 15 minimis although theoretically incompatible, is a popular and probably useful addition to mixtures of this type.

In older people, or in a patient in whom it is desirable to

promote cough, the salts of ammonium are most useful, especially in the treatment of chronic bronchitis or of "winter cough," e.g.

R	Ammonii carbonatis	-	3-5 grains
	Tincturæ ipecacuanhæ		20 minims
	Tincturæ scillæ	-	10-15 minims
	Syrupi tolutani	-	30 minims
	Aquam chloroformi ad	-	1 ounce

Three times a day

Recent infusion of senega may be substituted for the chloroform water. In such cases, iodide of potassium is a favourite remedy, and most hospital pharmacopæias include an alkaline potassium iodide mixture. That in use at the Brompton Hospital may be quoted as an example —

R	Potassii iodidi	-	3 grains
	Ammonii carbonatis		3 grains
	Potassii bicarbonatis		15 grains
	Aquam chloroformi ad	-	1 ounce

For patients with much bronchial spasm or in asthmatic attacks, a useful mixture is —

R	Potassii iodidi		3 grains
	Potassii bicarbonatis		10 grains
	Ammonii carbonatis		3-5 grains
	Tincturæ stramonii		10-15 minims
	Syrupi tolutani	-	30 minims
	Aquam chloroformi ad	-	1 ounce

Other antispasmodics, such as lobelia, hyoscyamus, or belladonna, may be used instead of stramonium, and liquid extract of liquorice is often employed instead of tolu and chloroform water to mask the iodide and ammonium carbonate.

LINCTUSES

The usual dictionary definition of a linctus is 'a medicine to be licked up with the tongue.' They are generally small in amount, not more than a teaspoonful although usually containing powerful drugs, generally of anti-expectorant or sedative action. It is therefore desirable to explain to the patient that they are meant to be retained in the mouth for a short time and slowly swallowed. Their object is nearly always to allay or

suppress cough, and they are most frequently ordered at bed-time or for use during the night when an irritating cough causes wakefulness. The chief respiratory depressants and anti-expectorants are opium and its alkaloids, particularly morphine and codeine and certain derivatives of these, notably heroin, dilaudid, and dicodid. They all act by depressing the cough centre, but unfortunately they are equally effective on the respiratory centre and must therefore be used with caution. A. J. Clark (1940) gave a useful table with the relative depressant effects on the respiratory and cough centres, as determined by pharmacological experiments. Morphine and dicodid seem to be about equal in effect, codeine only a quarter or at most a half as effective, dilaudid three-quarters whereas heroin is twice as powerful, possibly even more in its action on the cough centre, although this is doubtful. Dilute hydrocyanic acid was formerly believed to be sedative, and still finds place in some linctuses. Examples may be given —

Linctus codeinæ phosphatis (Brompton Hospital)

R. Codeinæ phosphatis	1/8 grain
Acidi citrici	1 grain
Glycerini	20 minims
Syrupi -	20 minims
Emulsionis chloroformi B.P.C.	2 minims
Aquam destillatam ad	60 minims

Linctus morphinæ (Brompton Hospital)

R. Morphinæ hydrochlorid	1/8 grain
Acidi hydrocyanici diluti	2 minims
Oxymellis scillæ	20 minims
Aquam destillatam ad	60 minims

Linctus diamorphinæ (heroin)

R. Diamorphinæ hydrochloridi	1/8 grain
Aceti scillæ - - -	15 minims
Syrupum pruni serotinæ ad	60 minims

The British Pharmacopœial Codex contains some useful linctuses notably *Linctus codeinæ* B.P.C., *Linctus diamorphinæ* B.P.C., and *Linctus diamorphinæ et thymi* B.P.C. The proprietary preparations, compound syrup of cocilliana, and citronin of Parke, Davis & Co., contain small doses of ethylmorphine and are often used as linctuses.

When any anti-expectorant or respiratory depressant preparations have been given to secure an undisturbed night, it is often necessary to give some hot drink in the early morning, or the Brompton Hospital hot-water mixture to promote expulsion of the night's accumulation. Great caution is necessary in the use of respiratory sedatives in young children, old people, and in any patients to whom powerful hypnotics have also been given.

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CHAPTER V

THE SOLANACEOUS ALKALOIDS AND THE RELIEF OF SPASM

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CHAPTER V

THE SOLANACEOUS ALKALOIDS AND THE RELIEF OF SPASM

S PASMODIC contraction of smooth muscle in hollow internal organs gives rise to several distressing conditions. Thus asthma is due to spasm of the bronchiolar musculature, renal and biliary colic to irregular vigorous contractions of the ureteral muscle and of the bile duct or, more probably, of the gall-bladder, respectively. Again the abdominal pain, so often associated with diarrhoea, is due to a similar condition in the smooth muscle of the intestine.

The *causation* of such spasmotic contraction may vary in nature. Over-stimulation of the skin may produce, through reflex action, marked activity of the gut. On this depends the old fashioned use of external application of croton oil to induce purgation. Again, stimulation of the autonomic ganglion cells may result in a spasmotic contraction of most of the muscle of the alimentary tract, as is seen in acute nicotine poisoning. Violent contractions of the intestinal muscle follow excessive stimulation of the motor neuro-muscular junctions. Hence arises the vigorous purgation of acute muscarine poisoning. Direct stimulation of the plain muscle fibres themselves may be followed by vigorous and spasmotic contraction, as e.g. in lead colic or in the effects of posterior pituitary extract on the uterus. Finally, in those organs which are endowed with the power of peristaltic contraction, such as the intestine, the ureter, and, possibly, the bile duct, there is a local, as opposed to a central, reflex mechanism lying in the wall of the organ, Auerbach's plexus in the case of the gut. Through this plexus, over-stimulation, as from an irritant substance in the lumen of the intestine or a tiny calculus in the ureter, may give rise to an excessive muscular response in the organ, even

when all connexions to the central nervous system have been severed

In any such condition there are several general lines of *treatment* which may be adopted, all having as their object the reduction of these excessive contractions and consequently of the pain. Of these the simplest is to attack the effector mechanism at its most peripheral point. A drug which possesses the power of depressing muscle fibres, by direct action on them may be employed. Thus, renal colic may frequently be relieved by papaverine and asthma by inhalation of amyl nitrite.

The innervation of the smooth muscle of the internal organs is generally two fold in nature there being both a motor and an inhibitory nerve supply. It should be remembered that one of the most characteristic properties of smooth muscle, as opposed to striated, is its inherent power of rhythmic contraction and relaxation. The nerve supply does not initiate these movements but merely controls their extent, the motor increasing, the inhibitory decreasing the range of movement. Depression of the muscle fibres, whether by direct action or indirectly through stimulation of the inhibitory mechanism, will reduce or even abolish the normal movements of the organ, a result which may not necessarily be desirable. On the other hand, paralysis of the motor mechanism will not stop the normal movements of the muscle but will abolish any excessive degree of the contractions which may be caused by direct or reflex stimulation of that mechanism. The retention of the regular range of contraction and relaxation may be of advantage in treatment.

When this dual innervation is considered in more detail it is found that, apart from the blood vessels and the uterus, the motor side takes its origin chiefly in the cranial and pelvic nerves, forming the so called "parasympathetic" division of the autonomic system. Thus the constrictor pupillæ obtains its motor supply from a branch of the third oculomotor, nerve. The alimentary tract and those organs which are, developmentally speaking, outgrowths from it, the lungs and the biliary tract, receive their motor supply from the vagus and pelvic nerves. The ureters and the urinary bladder, apart

from the sphincters, receive fibres from the parasympathetic system which in the bladder are certainly, and in the ureter probably, motor in function The uterus, on the other hand, receives its whole supply, both motor and inhibitory, from the nerves of the lumbar outflow, forming part of the "sympathetic" division of the autonomic nervous system

The subdivision of the autonomic system into the two divisions, parasympathetic and sympathetic respectively, although convenient anatomically, is not functionally accurate. The means of transmission of the nervous impulse from the anatomical nerve end to the muscle fibre was long a matter of dispute. Dixon many years ago suggested that some substance elaborated at the nerve ending in response to the nervous impulse might in its turn affect the muscle, but this was left to Loewi to prove. He gave convincing evidence that stimulation of the vagus trunk gave rise, at the post ganglionic terminal, to the production of a labile substance, acetylcholine, which caused the inhibition of the heart. This work has since been extended to all terminals of this system. Again, Loewi produced evidence that on stimulation of the sympathetic nerves a substance, adrenaline-like in nature but which has never yet been definitely identified, is produced at the terminals and acts upon the muscle fibres. In consequence of this work, Dale has divided the autonomic nervous system into a "cholinergic" and an "adrenergic" moiety, according to the nature of the transmitting agent produced. Generally, these correspond to the older sub-divisions, with some exceptions, e.g. the sweat glands are innervated by the sympathetic system, but these nerves are cholinergic in character.

Thus spasmotic contraction of smooth muscle can be antagonized by direct depression of the fibres, by stimulation of the inhibitor or by paralysis of the motor terminals. Evidently the first of these methods would have the widest application if only the necessary drugs were available. Again, the second method could, and in fact can, be widely utilized owing to the fact that, in those organs in which spasmotic contraction is likely to occur, the inhibitor terminals are usually adrenergic in character and can therefore be stimulated by a sympatho-mimetic drug.

such as adrenaline, ephedrine or benzedrine. The utility of the method is, however, limited in practice, owing to the side-actions of these drugs, e.g. the rise of blood pressure due to adrenaline, the effects on consciousness of ephedrine and benzedrine. The third line of attack is necessarily more limited in scope, as it can be employed satisfactorily only in those cases in which the spasm is caused by stimulation of the motor nerve ends, either reflexly or direct.

THE ANTI-SPASMODIC ACTION OF THE ALKALOIDS

It has long been known that certain alkaloids possess the power of abolishing the normal results of stimulation of the vagus. They are derived from a number of plants of the solanaceous (potato) order, belladonna, hyoscyamus, datura, duboisia, mandragora. Mandragora and hyoscyamus certainly, and belladonna possibly, were known to the ancients, Dioscorides, Galen, and others. Datura was probably introduced by the Arabian physicians. Duboisia is an Australian genus and is a recent introduction. Many alkaloids have been described but, of the earlier, many such as "duboisine," "mandragorine" are mixtures only. The pure alkaloids are hyoscyamine and hyoscine (scopolamine), both existing in three forms, two optically active isomers—the dextro- and laevo-rotatory compounds, and a third, optically inactive, being a mixture in equal parts of the d- and l-forms, these being atropine and atroscine, respectively. Of the two optically active isomers, in both cases the l-form possesses much more action on the nerve terminals than the d-, whereas both isomers possess about equal activity on the central nervous system.

Broadly speaking these alkaloids have these two general sites of action—on the central nervous system not being discussed here, and on the peripheral terminals. Again, in the pure form, hyoscine is rarely used for its peripheral action, although the galenical plant preparations will contain it in greater or less amounts. For the present purposes it will suffice if the action of atropine alone is discussed, although hyoscyamine, atropine, and hyoscine all occur in the ordinary preparations employed.

ATROPINE THERAPY

So far as the peripheral actions are concerned, the effects produced by atropine are exactly similar to those resulting from section of nerves of cholinergic function. Thus, after atropine, stimulation of the vagus trunk in the neck is no longer followed by a fall in blood pressure and slowing of the heart. In earlier days this was explained by saying that atropine "paralyses the nerve terminals." It is now known that this is not entirely accurate as, even after atropine has been given, it can be shown that on stimulation acetylcholine is still produced at the nerve terminals, which are therefore clearly *not* paralysed. Atropine acts by preventing acetylcholine from obtaining access to those receptors in the muscle fibres upon which it normally acts. Thus the result is that the cardiac or other muscle fibres are prevented from responding to the normal cholinergic stimulation.

In addition to this action on the neuro-muscular mechanism, it can be shown that atropine possesses also, although only in low degree, the power of directly depressing smooth muscle. It can, for example, antagonize the action of histamine on isolated strips of intestine. It is improbable, however, that this action is of any importance therapeutically.

ASTHMA — The beneficial action of atropine in spasm of smooth muscle is therefore likely to be shown in those cases, and those alone, in which the muscle obtains a motor supply with cholinergic affinity. These muscles are to be found in the bronchioles, the intestine, the ureter, the bladder, and the biliary tract. Taking the bronchioles first, it is an old treatment, but still in use, to advise smoking of cigarettes prepared with stramonium leaf. It is believed that small traces of alkaloids are present in the smoke and can be absorbed from the respiratory passages. It is perhaps more likely that the principal action is due to a reflex inhibition of the muscle from the nature of the smoke. Better, probably, is the administration of fairly full doses of the tincture of belladonna or stramonium shortly before bedtime. On the whole, however, it must be admitted that in the majority of cases of asthma the

exciting cause is of an allergic nature and the spasmodyic contraction due to a direct stimulation of the muscle fibres themselves. It is therefore unlikely that atropine will often be of much value. *Adrenaline* or *ephedrine* will probably prove more effective, but to avoid the results of frequent administration of these drugs *belladonna* or *stramonium* may be tried instead.

Perhaps a few words on *lobelia* may not be out of place, as it has long been used in the treatment of asthma. Its active principle, a lobeline, resembles nicotine in action rather than atropine. It stimulates respiration and has been used, often with success, in the treatment of acute respiratory failure, e.g. narcotic poisoning. By mouth, however, the drug generally used as the ethereal tincture, acts as an expectorant, chiefly by irritating the gastric mucous membrane like ipecacuanha, and possibly by an action on the vomiting centre, like nicotine. It has been used therefore in a number of respiratory conditions. Apart from a reflex inhibitory action through its nauseating properties, on the muscle of the bronchiole it is doubtful if the drug is of any real value in asthma.

INTESTINAL COLIC—Apart from chronic lead poisoning intestinal colic is rarely a source of more than discomfort. None the less the griping which follows the taking of an irritant substance, such as a drastic purge, may be sufficient to call for alleviation. Again, diarrhoea from any cause, e.g. unripe fruit in the young or the results of bacterial action on food residues in the gut may be accompanied by colic. In these cases it is evidently desirable that peristalsis should continue so that the cause may be removed. For this reason, *belladonna* is to be preferred to drugs which would check the gut movements, such as opium. The tincture is useful and may be combined with a carminative to allay the "queasy" feelings in the stomach. An antacid may be added as in the following prescriptions—

R	Tinct belladonnae-	-	-	10 minims
	Syr menth pip			60 minims
	Bism oxycarb	-	-	20 grains
	Aquam ad	-	-	½ ounce

R	Tinct hyoscyam	-	-	-	-	20 minims
	Syr zungib	-	-	-	-	60 minims
	Magn ox lev	-	-	-	-	30 grains
	Aquam ad	-	-	-	-	½ ounce

In this kind of case there is no necessity for a rapid, intense action but rather the reverse. This is obtained by the use of a galenical preparation, rather than a pure alkaloid.

RENAL COLIC—In renal and biliary colic, pain may be intense and a rapid, powerful action is wanted. Certainly there is good experimental evidence that, in the latter condition at least, morphine is not desirable, as it causes a further contraction of the musculature. None the less, owing to the intensity of the pain, it may be necessary to give an injection of morphine or, probably better, of diamorphine (heroin). It is most advisable, however, to combine this with an injection of atropine $1/50$ grain even up to $1/30$ grain of the sulphate. The larger dose should not be repeated within four or six hours.

Perhaps *nocturnal enuresis* can scarcely be considered as a condition of spasm of the bladder. It is, however, often due to a state of enhanced irritability of that organ, although there may be in addition a psychological basis in some cases. It is an old, and frequently successful, treatment to administer the *tincture of belladonna* by mouth in gradually increasing dosage until the child shows, or complains of, a dry mouth. Incidentally, it may be noted that children show a higher degree of tolerance to atropine than do adults when judged on a weight or age basis.

OTHER CONDITIONS—There are certain other conditions in which the anti-spasmodic action of atropine may be useful. Thus, in *muco membranous colitis*, spasm of the colon may be pronounced and can be well treated by tincture of belladonna, in doses of, say, 10 minims thrice daily.

In *peptic ulcer*, also belladonna is often useful but whether by its action in reducing the acid secretion of the stomach or its movements is by no means certain. In this condition there is evidence that the drug loses its efficacy after a period of time, and so either the dose should be increased or the treatment changed.

SKELETAL MUSCULAR SPASM—So far consideration has been confined to spasm of smooth muscle. Tremors and rigidity appear in the skeletal muscles in the Parkinsonism of late *encephalitis lethargica* and may, indeed, become completely crippling. Experience has shown that the solanaceous group of drugs, more especially perhaps stramonium, are effective in treatment. Large doses must be given, and it is generally found necessary to increase them with the passage of time. *Hyoscine hydrobromide* may be employed, starting with a dose of $1/150$ grain subcutaneously and increasing as found necessary. The explanation of the action is not yet clear. The rigidity is believed to be of extra-pyramidal origin arising probably in the mid brain. Presumably the action of the drugs must be in the same place but, apart from their action on the cerebral cortex and medulla, little is known as to the effects of these drugs on the brain. Hyoscine, in medicinal doses, exerts a depressant action on the motor cortex, whereas atropine is excitant. In preparations of *stramonium* both hyoscine and atropine occur, but generally there will be sufficient of the latter to counter-balance the effects of the former at this point. It is not likely that the benefits induced by these drugs can be explained by their known actions on the cerebral cortex. In this treatment, such large doses are commonly required that the first signs of toxic effects are often induced.

TOXIC REACTIONS

So far as the peripheral effects are concerned the toxic actions of all the solanaceous alkaloids are similar. The first results are, as a rule, dryness of the mouth and skin, difficulty in swallowing, and acceleration of the heart rate. Next come indistinctness of vision and flushing of the face. None of these is evidence of serious poisoning and, certainly in Parkinsonism, it may be necessary to push treatment to this extent, although for other conditions such a degree of toxic effect is certainly undesirable. The more serious symptoms arise from the action on the central nervous system. With atropine, these take the form of garrulousness, excitement, muscular twitchings, even convulsions, all arising from stimulation of

the cortex. With hyoscine, the effect of moderately large doses on the central nervous system is to increase the depression of the cortex, with sleep. But larger doses still, it is said, may cause excitation as with atropine.

General poisoning with these alkaloids as a rule follows oral administration, but local application may produce serious effects. These have occurred after the over lavish use of atropine drops in the conjunctival sac. If too much is used the excess may drain away down the lacrymal duct and be absorbed from the nasal cavity, thus giving rise to general poisoning. It may be pointed out perhaps that the instillation of two drops of a 2 per cent solution into each conjunctival sac means that about $1/16$ grain has been used nearly four times the maximal B.P. dose. It is not difficult to understand that severe poisoning may arise in this manner.

In connexion with this local use of atropine there is one special danger to be borne in mind—the risk of causing acute glaucoma. With the dilatation of the pupil the iris is drawn out to the periphery and hinders the passage of fluid through the canal of Schlemm. In the normal young individual the consequent rise in intra-ocular tension will not cause ill effects, but, in persons in whom that tension is already raised, there is a considerable danger of the development of an acute attack of glaucoma. Generally, it is a sound rule to use homatropine in place of atropine in all persons over, say, forty five years of age. With this drug there is less tendency for this rise of intra-ocular pressure to occur and, should it do so, the instillation of physostigmine will cause the pupil to contract and so remove the risk. Physostigmine is not able to antagonize fully the effects of atropine.

CHAPTER VI

DRUGS USED IN THE TREATMENT OF GASTRIC DISORDERS

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CHAPTER VI

DRUGS USED IN THE TREATMENT OF GASTRIC DISORDERS

AN essay confined to the true diseases implicit in the above title must be limited, because the true diseases of the stomach are few, and the drugs with any action upon gastric tissue in a direct manner are also not numerous. But if it can be accepted that the disorders of the stomach may include every disease which is likely to produce spasm of the pylorus, and that certain deficiency diseases, such as pernicious anaemia and sprue, depend for their existence upon defects of the upper alimentary tract, it becomes apparent that the subject is in reality a vast one.

There are really only three true diseases of the stomach—gastritis, peptic ulceration, and cancer—and diagnosis and treatment would be greatly facilitated if this fact were more frequently remembered. If, every time he were confronted with a case of dyspepsia, the practitioner would ask himself if it could be due to gastritis, ulceration, or cancer, and in the event of the answer being negative he would proceed to the conclusion that the disease must therefore be extra gastric, far greater exactitude would be achieved, with consequent benefit to the sick.

GASTRITIS

It is difficult to write of the treatment of gastritis unless the reader will accept as preliminary axioms that it is probably a rare disease, that its symptomatology is vague, variable, and seldom sufficient to call for treatment, and that it can never be diagnosed with certainty except by gastroscopy. For years gastritis has been used as an easy label by the incompetent, and the introduction of gastroscopy has indicated the measure of their inefficiency; it has further been demonstrated that gastritis may be present in severe degree in a patient having few

symptoms Anyone doubting this statement should recall that every patient with pernicious anaemia has chronic atrophic gastritis, and that it is a small proportion only of such patients who experience pain, indigestion, nausea, or other symptoms directly referable to the stomach The claims of radiologists to diagnose gastritis from certain appearances of the rugæ are not supported by those familiar with the use of the gastro-scope, and the usual technique of gastric analysis, unless reinforced by the examination of a series of samples withdrawn from the resting stomach does not give data on which a diagnosis of real accuracy may be made

TREATMENT —Clinical knowledge of gastritis is so limited that it seems almost futile to speak about the treatment of the condition But perhaps it is safe to say that when gastritis is suspected it is certainly wise to correct any habits, such as the excessive consumption of alcohol or tea which may have caused the condition or occasioned its continuance Diet, too, is important although I have never felt satisfied that the habitual prohibition of mustard, pepper, and condiments is more than a pious gesture It seems on the other hand, obvious that it is wise to prescribe, in every case in which the presence of an organic lesion in the stomach is suspected, a diet which will provide ample nourishment with a minimum of gastric work, this implies the exclusion of all foods which normally remain a long time in the stomach, and may be summarized as follows —

Diet —This must exclude all hard raw vegetable foods, such as salads, nuts, apples, pears, pineapple and pickles, all hard foods, such as tough meat, new potatoes and others of the harder cooked vegetables The best foods are nutritious fluids, such as milk and milk beverages in general soups of high calorie value, animal and vegetable fats, eggs, soft fishes, tender meat, poultry and game (especially minced), and light puddings and sweets Alcohol and strong tea are forbidden

Drugs —It has yet to be proved that any drug is of value in the treatment of the disease Lavage of the stomach, usually a procedure ineffective except to perpetuate a neurosis, may

bring relief in a genuine case of gastritis. A solution containing 60 grains of sodium bicarbonate to a pint of water will remove excessive secretion of mucus, and some authorities have claimed that a weak solution of hydrogen peroxide brings a relief which is not wholly due to suggestion.

In cases of acute gastritis, "the morning after the night before," it seems certain that colloidal kaolin, in repeated doses of a tablespoonful, is of real value.

GASTRIC ULCER

The *treatment* of peptic ulcer has been written about so constantly in so many medical journals that it would be inappropriate here to attempt anything like a full description of it. But it must be said, with all force, that there are few diseases in which treatment is more satisfactory, and that cases which fail to respond owe that result usually to carelessness on the part of the patient or insufficient care on the part of the practitioner. As with so many diseases, there have been numerous attempts to introduce short-cuts to success, with relaxation of tiresome but essential sides of the treatment and consequent failures. The most notable example of this in recent years has been the employment of *histidine* in the treatment of peptic ulcer; to the patient and, it is to be feared, to many practitioners there is a great temptation to adopt a treatment consisting of a series of injections with simultaneous relaxation of dietary precautions. I have seen a whole series of haemorrhages and serious relapses in patients who have abandoned the orthodox and commonsense treatment of a gastric ulcer in favour of injections of histidine. In saying this it is not suggested that histidine injections, whether given in the form called "larostidine" or otherwise, are without any value at all. Far from this being so I have several times had the impression that they have been of real service in bringing about improvement in an unusually resistant case. But I am entirely certain that such treatment must always augment and not replace the orthodox treatment by diet and the drugs which combat acidity.

Diet—The successful diets employed in the treatment of peptic ulcer are all alike in that they conform to certain main principles, they permit of full nutrition whilst calling for a minimum of peristalsis and, by their composition, tend to absorb the secreted hydrochloric acid. Milk remains the basic substance, and to milk may be added gradually such soft and nutritious foods as tapioca, rice, eggs, and cream. Feeds must be given at intervals not exceeding three hours and small meals introduced by gradual steps.

Drugs—Of the drugs employed to correct acidity, *belladonna*, or its active principal atropine, is not sufficiently used. It is probable that it is of slight efficacy unless given at a time when it will easily reach a considerable proportion of the secreting surface of the stomach. In order to achieve this it should be given in a single dose on waking in the morning, the following prescription being most suitable—

R	Tinct belladonnae	-	-	-	7 minims
	Aquam ad-	-	-	-	60 minims

A teaspoonful to be taken in 2/3 tumbler of warm water on waking.

Atropine is the only drug save morphine which will actually inhibit secretion, as opposed to the drugs which will neutralize or absorb acid.

The *alkalis* have so long and so rightly been recognized as of high value that it is not necessary to stress their use. Various formulae are employed of which I have found the following to have stood the test of time—

(1) R	Mag carb pond	-	-	-	2 ounces
	Mag carb lev	-	-	-	2 ounces
	Cretam præp ad	-	-	-	6 ounces

“The Strong Powder”, a teaspoonful to be taken, stirred in water, one hour after each meal and feed.

(2) R	Mag carb pond	-	-	-	-	1 part
	Mag carb lev	-	-	-	-	2 parts
	Cretam præp	-	-	-	-	3 parts

“The Weak Powder”, to be taken as directed.

The first of these prescriptions is of much greater neutralizing power than the second, but it is too laxative for most patients, who for this reason are usually best served by the second formula. Occasionally even the latter proves too relaxing, in which case it must be further diluted with chalk. Alkalosis is occasionally produced by such powders and scarcely any of them are immune from this risk. *Tribasic magnesium phosphate* has enjoyed a certain repute as being without such action, but it has been largely abandoned, as those using it found its gritty character undesirable.

In recent years the therapy of peptic ulcer has been notably improved by the employment of *colloidal aluminium hydroxide* as an antacid. It has been placed on the market by several firms of high repute and has been proved, by experiment and by experience, to have great value. It cannot produce alkalosis, it effectively corrects hyperacidity, and no ill effects are produced by excessive dosage. It has two disadvantages only—it is more costly than the ordinary alkalis, and it appears to be slightly constipating, the usual optimum dose is two or three teaspoonfuls after meals and feeds.

Tube-feeding—A further and even more important advance has been the wider employment of tube-feeding. By introducing a small flexible tube into the stomach through the nose it is possible, by means of an attached reservoir, to administer milk and other appropriate foods as a continuous small stream, and the addition of alkali or aluminium hydroxide ensures complete and constant neutralization. By this method it is not infrequently possible to bring about the healing of deeply penetrating ulcers of the stomach which had previously been susceptible to treatment by surgical resection only.

CANCER OF THE STOMACH

Medical treatment here remains at best palliative, and it is only necessary to remind the reader that gastric lavage will at times greatly increase the comfort of the patient. Anyone can pass a stomach-tube on himself after a few days, and a child's oesophagus-tube is usually sufficiently large to permit of proper lavage when the patient is on a fluid diet. In cancer

of the stomach it is rarely wise to permit anything but fluid food, and it should never be forgotten that *alcohol* is usually one of the most valuable articles of diet in this disease, the energy provided by the alcohol becomes of real value, and its sedative effect may add enormously to the comfort of the patient

The list of definite diseases of the stomach is now practically exhausted, but there remain certain obscure conditions to which allusion must be made

DISORDERS OF SECRETION

Excessive secretion is usually implied by those physicians who diagnose "*hyperchlorhydria*," but many who have made a particular study of gastro-enterology have long since abandoned the term. If a patient with *dyspepsia* is found, on gastric analysis, to show an unusually high concentration of hydrochloric acid in the stomach contents it is probable that if organic disease is present it is in the form of a *peptic ulcer*, in such cases the amount of acid secreted is actually not in excess of the full average of health, the concentration being an effect of hypertonus and the absence of regurgitation, these facts make clear the dangers inherent in the use of the term *hyperchlorhydria*. In certain rare cases a true excess of gastric secretion is found, but in these the concentration of acid is often not notably high, *gastro-succorrhaea* would be a more permissible term for this condition than *hyperchlorhydria*.

Treatment—In such cases it is often wise to employ alkalis or belladonna or aluminium hydroxide on the lines laid down in earlier paragraphs, provided it be remembered that *the more obvious the benefit that any given case of dyspepsia receives from alkali therapy, the more probable is it that the case is one of gastric or duodenal ulcer*. The importance of this rule lies in the fact that the better any such response to treatment, the more important is it for treatment and precautions to be maintained long after the disappearance of all symptoms.

Excessive acidity is occasionally the result of *gastritis*. More frequently *gastritis* will diminish secretion, and often will arrest it to such a degree that there is complete *achlorhydria* or

even absence of both hydrochloric acid and of pepsin. In the latter circumstance the term *achylia gastrica* becomes appropriate. Gastritis being the cause, the treatment should logically be towards the cure of gastritis, but, as has already been indicated, this is usually an impossible task. It does not follow that these patients should have no treatment, many of them will show an anaemia, either of the macrocytic or of the microcytic hypochromic type. The first of these calls for liver extract, the second for iron. The administration of hydrochloric acid in such cases has long been popular, it is seldom of benefit. If, by rough calculation, the amount of HCl secreted by the normal stomach in response to a meal is calculated, it will be realized that any attempt to replace this relatively enormous amount by an acid solution taken with meals is quite impossible. If, on the other hand, the small amount of dilute HCl (B.P.) traditionally prescribed has, if any, real therapeutic value, it provides a valuable argument in favour of homoeopathy. But I believe that such administration of HCl is almost invariably futile.

An exception may perhaps be made in those rare cases in which achlorhydria is associated with post-prandial diarrhoea. A tumbler of lemonade containing acid sometimes appears to benefit these and it should be prescribed as follows —

B Acid hydrochlor dil

A teaspoonful to be taken in half a tumbler of glucose lemonade during meals

The remaining dyspepsias are all of extra gastric origin, and an attempt to classify them or to describe their treatment would require a volume. The true diseases of the stomach are few, and most of them are intractable, but the most common of all is peptic ulcer, and this disease is one of the outstanding examples of the maladies in which modern knowledge, correctly applied, yields extremely gratifying results.

CHAPTER VII

THE USE AND ABUSE OF APERIENTS

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CHAPTER VII

THE USE AND ABUSE OF APERIENTS

IT is a good sign of the times that the writer feels justified in hoping that it is not necessary to begin an article on aperients with a warning against excessive zeal in prescribing them. Nevertheless, old customs die hard, and those practitioners who were trained by supporters of what one author has called "ritual purgation" may be interested to know to what extremes the opponents of this ritual carry their heresy. So for their benefit it is proposed to begin with a few paragraphs on the misuse of aperients, putting forward some maxims and cautions which represent, not merely a personal opinion, for this by itself would not be entitled to serious consideration, but the teaching and practice of a large number of teachers of medicine and surgery. Any reader therefore who should find himself in agreement with heretical views expressed in these preliminary paragraphs can assure himself that, if he is erring in giving them his support, he is at least erring in respectable company.

SOME CAUTIONS AND MAXIMS

(1) It is unnecessary to begin the treatment of an acute fever, for example pneumonia or scarlatina, by administering an aperient.

(2) It is unnecessary, and probably harmful to administer aperients during the course of a long febrile illness. The constipation that accompanies such illnesses is harmless and, when the illness is over, a week or so later, no difficulty is found in getting the bowels to move again.

(3) No one has ever shown that a 'brisk purge' has any good effect in acute tonsillitis or any other acute inflammatory process.

(4) An initial purge is often recommended in the treatment of acute congestive heart failure, but experience has

shown that it can be omitted. If it is not necessary, then it is merciful to refrain from giving it to a dyspnoeic patient.

(5) The popular belief that a sick or sulky child should be "dosed" is stupid and a little dangerous. The claim is made that the child is often a great deal better after the aperient, but this is beside the point, for the sulks and minor illnesses of childhood *are* usually evanescent. The danger of these nursery doses lies in the possibility that the child's indisposition may be due to an abdominal pain about which he does not complain, as bitter experience has taught him that a complaint of a "tummy-ache" usually brings a dose.

(6) There is little need to emphasize the almost criminal folly of giving aperients to patients with undiagnosed abdominal pain or vomiting. It would be well if all medical students and nurses could be taught that aperients should be given only to those who are in good health and never in the expectation that they will set right some malady or ailment.

(7) The pre-operative purge of former days has been abandoned in most surgical units. The routine post-operative purge given three or four days after an abdominal operation has also been abandoned by many surgeons (it is especially dangerous after gastro-enterostomies), but unfortunately they do not always succeed in controlling the meddlesome activity of their nursing staff for strange though it may seem there are still clinics in existence in which ward sisters are allowed to prescribe aperients.

EFFECTS COMMON TO ALL APERIENTS

The classical division of aperients is into *Laxatives*, which increase the bulk of the stools but do not alter their consistency, *purgatives*, which produce unformed motions, *hydragogues*, which are followed by watery stools, *drastic purgatives*, which excite an inflammatory reaction in the intestine. This is not a bad classification, but it should be remembered that it is a classification based on the intensity of the effect produced by the drug, which depends not merely on the choice of the aperient but also on the dose given and the contents of the patient's colon.

Consistency of motion.—Any aperient tends to produce a stool which is more watery than normal, for by shortening the time taken for the journey through the intestine it reduces the time available for the absorption of water in the colon.

Gripping is the sensation of pain produced by over-vigorous muscular action in the intestine. Those vegetable irritants (aloes, cascara, rhubarb, senna, colocynth, podophyllum, and jalap) which act largely by direct stimulation of smooth muscle fibres, tend to gripe more severely than the aperients which increase peristaltic activity indirectly by increasing the bulk of the intestinal contents. But the latter too may gripe unpleasantly, especially if some resistance is offered to the passage of the fluid intestinal contents by an already formed faecal mass in the lower part of the large intestine.

The time of action depends to some extent on the contents of the intestine and the bodily exertions of the patient during the few hours after taking the aperient. The salines and castor oil act quickly, within a few hours, or sometimes within an hour; the vegetable aperients, as will be seen, are considerably slower.

THE CHIEF APERIENTS

The most useful classification of aperients is that which is based upon their mode of action :—

(1) Aperients which increase the non-absorbable bulk of the intestinal contents, and thus indirectly excite increased peristaltic activity.

(2) Aperients which directly excite increased peristaltic activity by means of an irritative action on the intestinal wall.

INCREASE BULK OF CONTENTS

Food and drink.—The hearty eater and drinker is rarely constipated. If the lesson taught by this fact is borne in mind no attention need be paid to "special diets for constipation," which tend to divert the patient's (and the practitioner's) attention from the important fact that quantity matters more than quality.

The dried seaweeds.—The most popular is agar-agar, which

is sold under a number of trade names. If swallowed dry it imbibes water like a sponge, but if already mixed with a liquid (as in some proprietary preparations) it cannot of course do so. Such dried seaweeds are satisfactory mild laxatives, and there is no objection to their use.

Liquid paraffin—When the oil is taken already emulsified (as in many proprietary preparations) the stools become slightly softer and more bulky on account of their admixture with the emulsified oil. When the oil is taken neat it still exerts a mild aperient effect although the exact mode of action is uncertain. It probably acts partly by virtue of its own mass and partly by interfering with the absorption of foodstuffs.

The salines—Magnesium and sodium sulphate, potassium sodium tartrate and basic sodium phosphate are the salines most used but it should be remembered that all the salts of magnesium exert an aperient action. The salines should be taken in watery solution on an empty stomach (for example on rising from bed) and the solution should be either hypotonic or isotonic, hypertonic solutions tend to excite pylorospasm with the result that the draught leaves the stomach slowly and vomiting may occur.

The salines owe their action to the fact that the salts themselves are so poorly absorbed by the intestinal epithelium, absorption of their water of solution cannot take place past the point at which further absorption would leave in the intestine a solution of higher osmotic pressure than that of the solutes in the tissue of the intestinal wall. A 6.5 per cent solution of magnesium sulphate is isotonic with human tissue-fluids and so if a draught containing two teaspoonfuls of magnesium sulphate is taken about four ounces of water will remain unabsorbed in the intestine to maintain the isotonicity of the magnesium sulphate solution. This unabsorbed water excites peristaltic waves which are transmitted to the colon and thus the contents of the colon too are hurried on even before the saline draught has reached the caecum. A large fluid motion is passed the volume of which is far greater than that of the original saline draught.

It should be noted that the aperient action of a saline amounts to this, that a certain volume of water is rendered non-absorbable by the intestinal epithelium. There is no evidence that magnesium sulphate exercises any direct action on the wall of the intestine, and it has been shown that little or no absorption of the salt occurs. It is interesting to note that when magnesium sulphate is injected directly into the circulation its effect is to produce narcosis, and in fact it has been employed for this purpose. It is a dangerous narcotic. The popular belief that the regular daily dose of a saline purgative is in some way deleterious is, of course, wrong. A daily dose of salts is an excellent way of securing a daily motion for patients who wish to aid Nature.

The sulphates and sulphonamides.—The notion that sulphates should not be given to patients who are being treated with drugs belonging to the sulphonamide group is almost certainly incorrect, and has just as little theoretical or experimental support as the *ipse dixit* that eggs too are incompatible with drugs of this group.

THE IRRITANTS

The drugs so classed are reagents which, when brought into contact with an isolated strip of intestine, excite muscular contractions. It is uncertain to what extent these irritants act directly on the smooth muscle and to what extent through reflexes evoked by stimulation of the epithelium or local nerve plexuses, for it is difficult to conduct decisive experiments to distinguish these modes of action. Senna has been shown to act directly on the isolated muscle-fibre, and probably other similar vegetable preparations do so too.

The anthracene group.—The chief members of the group are aloes, cascara, rhubarb, and senna. These act by virtue of several anthracene derivatives which they contain and which are so slowly set free from their combination in larger molecules during the passage of the drug through the intestine that the irritant action of the anthracene derivative is not exerted until the colon has been reached. Thus the action of this group is a delayed action, and the members of the group

are particularly suitable for use in "dinner pills" to be taken after the evening meal in expectation of a result in the morning. In fact this group of drugs could not be used with safety if the active principles were liberated high in the small intestine, for then these would be freely absorbed into the blood stream, and unpleasant and possibly dangerous toxic effects would be produced.

Pregnancy and the anthracene group—Violent purgation is probably always dangerous to some degree for the pregnant woman, but tradition has attached a special odium to the anthracene purgatives, and in particular to aloes. It is true that aloin (the active principle of aloes) when injected intravenously into laboratory animals causes violent contractions of the uterus, but it is most unlikely that the oral administration of an ordinary purgative dose can have any such effect in human subjects.

Castor oil is non-irritating until it has undergone lipolytic digestion in the small intestine. Being a compound of glycerol and a fatty acid (ricinoleic acid) it undergoes emulsification with bile salts and digestion with lipase just as butter does, and the ricinoleic acid thus set free is an irritant, as so many other fatty acids are (compare the laxative effect of a "rich" dinner). Castor oil acts in a few hours, and rarely if ever produces any tendency to subsequent diarrhoea, probably because the ricinoleic acid is absorbed into the circulation. It is likely that the constipating after-effect attributed to castor-oil is due to nothing more recondite than the thoroughness of the evacuation which it brings about. Castor oil is an excellent aperient with no disadvantages except that it is unpalatable, it may excite vomiting, even in those who find no difficulty in swallowing it, and is so thorough in its action that when misused (for example when administered to patients suffering from acute appendicitis) it may do much harm.

The drastic purgatives—These are vegetable products which contain reagents capable of not merely stimulating the wall of the intestine but of exciting an acute enteritis with a diarrhoea lasting for several days. The chief members of the group

are colocynth, jalap, and podophyllum, the active principles of which are glucosides split off from resins in the course of digestion

Croton oil, which contains a highly irritating resin, has been removed from the British Pharmacopœia, but it is still used in mental hospitals, as it has the merit of being tasteless when well mixed with food or drink. Among medical students it is the weapon chosen by the avenger who wishes to lay a trap for pilferers of his food supplies, the enteritis produced by a large dose may be severe enough to incapacitate the thief for several days.

The mercury compounds—Many physicians, including myself, never prescribe mercurial purgatives, calomel and metallic mercury. The objection to their use is that in some cases even a small dose may have an unpleasantly powerful and prolonged effect, and in other cases a large dose may be required to produce even a mild laxative action. The assertion that calomel is "cholagogic" and "antiseptic" is based solely on tradition and not on fact.

Phenolphthalein—This drug has the advantage of being tasteless, and has for that reason been recommended as suitable for children if given in the form of medicated sweets. It is also an ingredient in several proprietary preparations of emulsified paraffin and a number of proprietary pills. There are two objections to its use—first, it may produce an ugly, blotchy red rash and, secondly, it is easily absorbed and excreted again in the bile (compare the use of the iodine compound in radiography), with the result that its purgative action may be repeated for several days. The mode of action of phenolphthalein is similar to that of the anthracene group in that it is a direct irritant of the wall of the intestine.

STRYCHNINE IN PURGATIVE PILLS

Strychnine has no aperient action whatsoever, and yet this poison is to be found in many proprietary pills and in at least three B P C pills. It is not widely enough known that little children have been killed by swallowing a fistful of such pills in mistake for sweets, one American writer on therapeutics

goes so far as to assert that it is the most common mode of accidental strychnine poisoning. It is to be hoped that drug manufacturers will stop the reprehensibly ignorant practice of dispensing such a useless and dangerous poison as strychnine in conjunction with harmless vegetable aperients, and that all practitioners will do their best to prevent the occurrence of tragedies by ceasing to prescribe pills which contain even a trace of this convulsant.

THE ENEMA

The ordinary soap-and-water enema is not always absolutely safe and harmless, although as a general rule it is so. When the large intestine is ulcerated and its wall thinned, an enema may be just as dangerous as a purgative in appendicitis, and indeed in any case of suspected disease of the lower bowel the enema is a therapeutic measure which should be employed with the greatest caution.

Ulcerative colitis is a comparatively rare disease, and so practitioners who find themselves called upon to treat a patient suffering from it naturally turn to their textbooks for help. Among the treatments mentioned in textbooks is to be found regular washing-out of the colon, but many physicians, of whom I am one, have formed the opinion that these wash-outs are useless, add to the patient's discomfort and probably are harmful.

RECTAL CONSTIPATION

Rectal constipation, that is to say constipation in which the faecal mass reaches the rectum but is not passed through the anus, is not uncommon. The chief causes are muscular weakness and insensitiveness acquired through habit. A method of dealing with the trouble which sometimes succeeds in not merely relieving the patient temporarily, but in preventing recurrence, is the daily injection of glycerin, at first about one ounce, but less and less every day, after a short while some patients are cured or greatly improved. Digital breaking up of a rectal impaction is occasionally necessary in the old. There is no other way of dealing with a troublesome "lodgement," and the hardened mass which obstructs the anus by

acting as a ball-valve is usually surprisingly small Enemas and aperients are worse than useless in this condition

THE TREATMENT OF CONSTIPATION

(1) In *acute constipation*, that is to say in constipation of recent origin, aperients should be withheld until the physician feels absolutely certain that they will not do harm No patient ever died for want of an aperient

(2) In *chronic constipation* it is wise to assume that the patient who makes this his chief complaint has either got something more than mere constipation the matter with him or else has some reason for visiting the practitioner other than the wish to have an aperient prescribed Many patients consult a doctor about constipation because they fear that it may be a symptom of more serious trouble, many others wish for an opinion about their heart or their blood pressure, but are too apprehensive to ask for it directly In advising a patient found to be suffering simply from *chronic constipation* it is wise to begin by telling him three things —

(a) That *chronic constipation* does not poison the blood or lead to cancer, and is in fact a harmless inconvenience rather than a disease

(b) That plenty of food and drink, so far from being dangerous and tending to produce obstruction are Nature's method of ensuring regular motions

(c) That the regular taking of aperients is harmless The choice of the aperient and the frequency with which it is taken are matters for the patient's own taste and convenience

(3) Agar agar or some similar water-imbibing substance is the best aperient for those who find its feeble action adequate A saline draught in the morning is trustworthy and rapid Aloes, cascara, senna pods, and rhubarb are more variable in their effect, but can be taken at night and will not act until the following morning Castor oil is too nasty for most people, although it is trustworthy and effective, calomel is far too uncertain and, like the drastic purgatives, too liable to set up a short attack of painful diarrhoea

CHAPTER VIII

ASTRINGENTS

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CHAPTER VIII

ASTRINGENTS

"ASTRINGENT (1) Causing contraction and arresting discharges (2) An agent that arrests discharges Dorland's Medical Dictionary"

IT is in this wide sense of the term that the word astringent will be used here, and it will be taken as including any substance which tends to lessen the moisture of a mucous or of a raw surface. Such a result may be obtained by the coagulation of protein, or by the constriction of blood vessels or by simple absorption. There are two main groups of substances which have an astringent action—(1) a group of vegetable substances which contain tannic acid, and (2) certain salts of heavy metals. Both of these groups act by coagulating protein.

The *tannic substances*, when brought into contact with protein form a dense precipitate, insoluble in water. When tannic acid is brought into contact with a mucous or denuded surface it forms a tannate with the proteins of the tissues and its further penetration is prevented by the protecting coat thus formed. For this reason its action can only be local. The action, however, is felt on all the tissues and juices with which it comes into contact, and the function of cells is abolished, juices are coagulated, and secreting epithelium fails to secrete. Moreover, the blood in the capillaries in the immediate region is coagulated and a condition of thrombosis is produced. If congestion as part of an inflammatory process, is present, it is diminished or abolished. As tannic acid forms an insoluble tannate with certain metallic salts, and also with alkaloids, it is sometimes used as an antidote in cases of poisoning by such substances. Tannic compounds or tannins are widely distributed in the vegetable kingdom, and there are many vegetable substances which can be employed for their astringent qualities. The usual source of tannic acid is oak gall, but oak bark, krameria

catechu, kino logwood, and various other vegetable products have been used

Many *metals and metallic salts* are capable of acting on proteins, but the results differ greatly. In some cases the action is so severe that necrosis is produced, as with such caustics as silver nitrate, mercuric chloride, and arsenic, in others there is irritation varying in severity. In the group used as astringents a thin layer of an insoluble albuminate only is produced. The stronger astringents such as ferric chloride or alum, have also a haemostatic action due to their coagulation of blood in small vessels.

EXTERNAL ACTIONS

The action of all astringents caused by coagulation of protein by contact is purely local. It will be realized also that their use in therapeutics is limited to the relief of symptoms. They have no curative effect, and in some cases in which they have become popular they definitely delay the process of cure. Congestion is an essential part of the inflammatory process, and inflammation is essentially protective. Any quasi-therapeutic procedure which hampers inflammation otherwise than by removing the cause which has excited it is so far unscientific. Its only justification is in that small number of cases in which the symptom itself is so troublesome or exhausting as to demand relief even at the expense of some delay in the curative process. The protective coat produced on mucous or denuded surfaces may, for example, protect them from irritation and offer an obstacle to bacterial infection. The following are purposes for which astringents may be usefully employed —

- (1) To dry or harden the skin and relieve or prevent bed sores
- (2) To dry a weeping surface in various diseases of the skin
- (3) To relieve local oedema in the mucous membrane of the mouth or throat
- (4) To diminish secretion in the stomach or bowel
- (5) To lessen the bulk of a prolapsed rectum or to relieve bleeding piles
- (6) As antidotes in certain alkaloidal or metallic poisonings

THE SKIN — To keep the skin *dry* in cases of profuse sweating particularly in certain regions as between the toes

or in the folds of the axilla or groin or under the breasts, a simple astringent or absorbent powder, with a mild antiseptic added should be used. A similar procedure should be followed, combined with meticulous cleanliness in bedridden patients when soiling by the excreta occurs. The following is a suitable prescription —

R Zincı oxidı
Acidi borıcı H_3BO_3 - - - - 60 grains
Puly amyli - - - - - 120 grains

To *harden* the skin in order to prevent bed sores methylated spirit may be rubbed into the back, followed by vigorousunction of zinc ointment special attention being paid to the pressure points To a *weeping surface* astringents may be applied in the form of powders, lotions, creams, or ointments When there is much discharge frequent applications of an astringent lotion is often the best, for oily applications may dam up the discharge and prevent cleansing, and they prevent close contact of the astringent with the tissues The following may be used and should be applied frequently —

R	Liq plumbi subacet dil	-	-	1 ounce
	Zinci oxid	-	-	180 grains
	Mucil tragac		-	2 ounces
	Aquam roseæ ad	-	-	8 ounces

Pastes are less open to objection than ointments, as they form a porous mass which permits the passage of fluid, and they do not retain the heat to the same degree as ointments. The following is a mild astringent paste (MacKenna) —

R Zinci oxid
Pulv amyli ää - - - - - 120 grains
Paraff mollis - - - - - $\frac{1}{2}$ ounce

Zinc oxide, or calamine, an impure form of zinc carbonate containing much oxide, says MacKenna, is "the sheet anchor of the dermatologist," and he adds —

' the pharmacologists cannot explain why such an apparently inert inorganic compound should possess such curative properties. The

beneficial effect is probably due to the fact that calamine does not irritate the skin but when incorporated in a lotion it keeps the inflamed area cool and allows the natural resistance of the skin to function under the best conditions that are available."

BURNS—In recent years tannic applications have become the favourite treatment in the hands of many surgeons for *burns and scalds*. A 2 per cent solution of the acid is employed, and it is applied as a compress or as a spray. The patient should either be under an anæsthetic or well under the action of morphine, as otherwise the process is very painful. Romanis and Mitchiner describe the application of compresses as follows—

"A very thorough cleansing of the burnt area is necessary if subsequent infection is to be avoided, this should be performed by thorough washing with soap and water applied with a swab (never with a nail brush), especial care being devoted to the edges of the area. All blisters and dead and raised skin must be removed and the area ultimately swabbed over with ether to remove all natural or applied grease. The final application of tannic acid 2 per cent solution, is then made as a compress by applying several layers of gauze or lint soaked in the solution, these are laid evenly on the area and bandaged lightly but firmly in position. The compress is left undisturbed for two or three weeks and then removed when the scab comes away leaving epithelialized tissue in the case of first, second and third degree burns, and a clean granulating ulcer in more severe cases."

The spray method can be employed only when an electric cradle is available. The burnt area is sprayed with the 2 per cent solution and dried under the cradle, and the spraying is repeated hourly for twelve or eighteen hours, the drying being continued. The crust of tannic acid and protein separates in about fourteen days, sepsis rarely occurring.

In the mustard-gas burns which became familiar during the last war—and may become so again in the present—the following cold cream was found soothing and protective—

R Zinc Oxidi	-	-	-	-	-	360 grains
Oil lavandulae	-	-			-	30 minims
Pulv tragac	-				-	360 grains
Adip lanæ hydr	-				-	240 grains
Liq calcis ad	-	-	-	-	-	6 ounces

INTERNAL ACTIONS

THE MOUTH AND THROAT—Inflamed or œdematosus tissues of the mouth or throat are often much relieved by astringents “Boggy gums” are reduced by direct swabbing with tincture of myrrh. For the throat, one part of the glycerin of tannic acid with three of water causes a rapid subsidence of œdematosus swelling. Such a preparation is often given as a gargle, but it is much more efficacious if swabbed on the fauces with pledgets of cotton-wool, the application to be repeated frequently.

GASTRIC SECRETION—By their actions on the proteins in the food astringents render peptic digestion more difficult and, at the same time, by their action on the mucous membrane of the stomach, they diminish the secretion of gastric juice or irritate the mucous membrane. This latter effect is seen if a preparation of perchloride of iron is given by mouth, and gastric discomfort is a frequent accompaniment of iron medication. The only exception to this statement concerning astringents in gastric therapeutics is *bismuth carbonate*. This salt is never a powerful astringent, and its undoubted sedative action in gastritis is as much due to its forming a protective layer on the mucous membrane as to any coagulative power on the tissues. When it is desirable to lessen gastric secretion, as in peptic ulceration, it is best done by dieting measures or by giving a protective fluid, such as olive oil, which inhibits secretion, or some weak alkali. If such measures fail, small doses of atropine are almost always successful. A dose of 5 or 10 minims of the *tincture of belladonna*, given once a day, is usually adequate, it is best given before the first feed in the morning. In addition to inhibiting secretion it has the advantage of diminishing muscular activity in the stomach wall and in particular of relieving spasm of the pylorus.

DIARRHŒA—Formerly, astringents were regarded as the natural and proper treatment of diarrhoea, whatever its cause, but nowadays diarrhoea is regarded as being in most cases an attempt to rid the body of irritating or toxic matter, and treatment is directed towards aiding that process, rather than

towards balking it. Nevertheless, cases occur in which diarrhoea is so exhausting by dehydration, or so fatiguing by the activity it causes, that it necessitates symptomatic treatment. In such cases, however, it is better to diminish peristalsis and thereby limit intestinal discharges, than to attempt to prevent secretion by the mucous membrane. The drug of choice is, of course, *opium* or its alkaloid *morphine*. Morphine may be given to an adult by injection, or opium may be administered by mouth. McNee recommends the following prescription —

B Tr opiu-	-	-	40-80 minims
Tr catechu-	-	-	1 ounce
Mist crete ad	-	-	8 ounces

One ounce two-hourly or as required

This mixture not only inhibits peristalsis by the action of the opium but inhibits secretion by the action of the catechu (which contains tannin) and the chalk.

When tannin-containing drugs have been employed, the tinctures of *catechu*, *kino*, and *krameria* have been most in use, either singly or in combination or, as above, in combination with opium. They are now little used. In recent years several attempts have been made to obtain tannic acid compounds in a form which will resist solution in the stomach while undergoing solution in the intestine. Such are the preparations known as *tannalbin* (a tannate of albumin) and *tannigen* (acetyl tannic acid). Other preparations combine an antiseptic, such as formaldehyde with the tannin, but such an antiseptic is too irritating and most others would be ineffective. The position as regards tannic compounds in intestinal therapeutics has been tersely stated in the words — "Tannic acid in mild cases of diarrhoea is unnecessary and in severe cases useless."

GASTRO-INTESTINAL INFECTION — Of a different class from the drugs which have been considered, and an absorbent rather than an astringent, is *kaolin*. Kaolin and certain other inactive substances, such as charcoal, chalk, starch, and talc, by the simple absorption of water, tend to dry moist surfaces. But they have a further action. They adsorb

substances dissolved in the fluid, and prevent their absorption by the mucous membrane. This has been specially established in the case of bacterial toxins. Bacteria themselves may be fixed by these adsorbents and infection thereby diminished. Kaolin, in particular, is useful in various gastro-intestinal infective disorders. In *bacterial dysentery* large doses of kaolin—up to one ounce—have been recommended to be given mixed with porridge or stirred into hot tea. Such a dose should not be repeated frequently or the substance may collect in the bowel and cause obstruction.

HÆMORRHOIDS—The official suppository of tannic acid, on account of its styptic action, is of use in the treatment of *bleeding piles*, or a solution of tannic acid may be used to reduce the size of a prolapsed rectum.

THE RESPIRATORY TRACT

Astringents have no place, or a very small one in the therapeutics of the respiratory tract. Unfortunately, however, the vasoconstrictor *ephedrine*, in one or other of many commercial preparations pushed on the profession, has become popular in the treatment of *nasal catarrh*. When applied locally in the form of a spray or unguent or jelly such preparations have a rapid and dramatic effect, due to the intense vasoconstriction produced by ephedrine inhibiting secretion and causing a rapid drying of the mucous surfaces. But the vasoconstriction has prevented the active blood supply which is an essential part of the inflammatory protective process, and therefore, from any other than a symptomatic point of view, the result is undesirable. The symptom is relieved but the disease is prolonged. It may occasionally, although very rarely, be desirable to check excessive secretion of the bronchial mucous membrane. It sometimes happens that the breathing of a young child, suffering from acute bronchitis, is incommoded by an undue collection of fluid secretion in the bronchi, and the obstruction thus produced is increased by the catarrhal swelling of the mucous membrane. None of the ordinary astringents can be of any use in this condition, but small doses of atropine give relief, not only by inhibiting secretion but by causing dilatation.

of the bronchi, moreover, atropine is a respiratory stimulant. Griffith and Mitchell advise that enough should be given to stop just short of flushing of the face, and they recommend a dose of $\frac{1}{5000}$ to $\frac{1}{1000}$ of a grain to be given every three hours to a child of from one to three years of age.

TANNIC ACID AS AN ANTIDOTE

Lastly, it remains to speak of the use as an antidote of tannic acid, or any of its compounds, in cases of poisoning by an alkaloid or a metallic salt. The tannic acid forms insoluble compounds with such substances in the stomach or bowel and therefore delays absorption. As the compound so formed may undergo decomposition by the digestive juices the precipitated material must be removed or the poison may be absorbed later. Its use therefore is to give time by delaying absorption. When it is to be used the stomach should first be washed out, and then the tannic acid administered in repeated doses of 30 grains dissolved in a wineglassful of water. Or the stomach may be washed out with a solution of tannic acid in water, four ounces to the pint, with strong, stewed tea. In particular this line of treatment is adopted in cases of poisoning by atropine or belladonna and the allied drugs, by antimony, and by zinc chloride.

CHAPTER IX

CHOLAGOGUES AND DRUGS ACTING ON THE LIVER

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CHAPTER IX

CHOLAGOGUES AND DRUGS ACTING ON THE LIVER

IN the old days, when "a sluggish liver" was one of the most common of minor diagnoses, cholagogues loomed large in the pharmacopoeia. After a period of neglect, there are signs of a return of interest in this group of drugs, an interest which reflects the modern tendency to attribute once again a good many indefinite disorders to deficient activity of the liver. Migraine, for instance, which used to be "a bilious headache," is being more and more associated with failure of either the liver or the extra-hepatic biliary tract ever since the French description of "migraine biliaire" or "duodénale" drew attention in this direction. And just as there seem to be allergic factors in the causation of migraine, so the rest of the possibly allergic disorders are beginning to be suspected of hepatic origin. Instances of a possible hepatic factor in diseases associated with, or due to, metabolic disorder might be multiplied indefinitely.

One of the first results of this renewed interest has been the separation of the "cholagogue" drugs into two groups — (1) Drugs which cause an increased secretion of bile by the liver, which are referred to as choleretics (on the analogy of "diuretics"), and (2) drugs which empty the gall bladder and so cause an increase of bile-flow into the intestine without necessarily increasing the amount secreted to which the word cholagogue is restricted.

The second important modern change has been the understanding that in gall stone formation (at any rate so far as concerns the common and clinically significant type, the multiple faceted stone), it is not so much an increase of cholesterol in the bile which does harm, as a decrease in the bile-salt content. The bile salts keep the cholesterol in solution and so long as it is kept in solution it can cause no trouble. For

thus reason, the bile-salt content becomes the important factor. It is also important in the case of pure cholesterol stones, even if these are the result of an increase in the absolute quantity of cholesterol in the bile.

The third important principle is the appreciation of the fact that so-called biliary stasis, the failure of the gall-bladder to empty properly, is very rarely the result of weakness to be treated with stimulants of gall bladder contraction, but is usually caused by reflex spasm which prevents the outflow of bile, and which is properly treated by continuous sedative therapy.

With these three principles in mind, it is possible to apply treatment much more rationally. Choleretics are indicated when there is reason to believe that the secretion of bile needs stimulation, bile salts should be given when it is desired to make the bile a better solvent for cholesterol (or, of course, a better digestive juice for the absorption of fats, sterols, and fat-soluble vitamins). Cholagogues, in the strict sense, are rarely to be recommended but, to flush the biliary system or to relieve obstructions, sedative treatment is often most effective.

CHOLERETICS

What then are the genuine choleretic drugs? From the vast volume of work done on the subject and the enormous number of drugs investigated, one group stands out in efficiency—the *bile acids*. They are, without doubt, the most powerful choleretics available, they increase both the quantity secreted and also the bile salt concentration of the bile. That this is a most fortunate combination of effects is obvious. There are many bile acids natural and synthetic, from which choice may be made. *Taurocholic acid* and *glycocholic acid* or preparations of bile, are effective but not so good as *desoxycholic* or *dehydrocholic acids*. All, however, except dehydrocholic acid increase the absorption of sterols from the intestine, indeed it is said to be as easy to increase the cholesterol content of an animal by administering bile acids as by feeding it on cholesterol. Therefore if an increased absorption of fats and sterols from the intestine is wanted, rather than a change in the com-

position of the bile, one of the two common bile acids, or desoxycholic acid, is indicated. If, on the other hand, choleresis without increased absorption of cholesterol is required, dehydrocholic acid should be chosen. Its sodium salt, often called by its trade name of "decholin," is efficient, non-toxic, suitable for intravenous administration if necessary (it is commonly used for estimating the circulation time), and can be given conveniently in 10-grain doses by mouth after each meal.

Details about all the other reputed choleretics and cholagogues can be found in Sobotka's "Physiological Chemistry of the Bile," but one or two are worth mentioning here. Sodium salts are useless, but potassium salts are choleretics. Of the salts, the natural Carlsbad Sprudel salt is much the best. Increased water intake, so far from increasing bile secretion, seems to diminish it, and the argument by analogy from diuresis is quite unsound. A high protein diet increases bile secretion, carbohydrates do not. Alcohol and narcotics generally cause a decrease, but avertin increases bile secretion. Salicylates increase the volume of bile produced, but diminish its total solids. The purges, including calomel, have little or no effect, but oil of peppermint, dandelion, and radish are all choleretic.

CHOLAGOGUES

With regard to the emptying of the gall-bladder (pure cholagogue action) in normal subjects, magnesium sulphate, fats, eggs, vegetable oils and tagal stimulant drugs all have the effect of rapidly emptying the gall-bladder. Even the hypnotic suggestion of appropriate foods is effective, and the emotions control the activity of the gall-bladder to a considerable extent. Wittkower found that whereas fear and joy increased bile flow, anger stopped it completely. It is well known that a meal eaten in anger is badly digested, and there are people with "bilious tempers" who make themselves ill by being angry about their food. In patients with gall-bladder disease, stimulation of any kind usually has the effect of causing a complete spasm which arrests bile-flow (this, of course, is why such substances often precipitate an attack of gall-bladder pain).

Proper sedative treatment with belladonna will, however, restore a more normal state, in which it is often beneficial to give, for example, a dose of fat last thing at night, or of magnesium sulphate in the morning. But it is worth while to remember that, unless the patient needs the extra nutrition, there is no need to stimulate the gall-bladder with fats, it empties itself perfectly well in a state of comparative inertia, provided spasm is eliminated.

SEDATIVE TREATMENT

The proper way to ensure that the gall-bladder empties in patients suffering from cholecystitis or gall-stones is to eliminate reflex spasm. If all the musculature of the extra-hepatic biliary tract is relaxed, bile can pour out from the liver under its own secretion pressure, and the gall-bladder itself will almost empty by virtue of its elastic fibres. Complete paralysis would, it is true, lead to a passive distension, but complete paralysis cannot be produced by medication. The best sedative is *tincture of belladonna*. The natural alkaloids in the tincture are better than atropine, which is racemic and not laevo-rotatory. The only essential in treatment with belladonna is to find out the correct dose for the particular patient. It is universally recognized that the proportional dose for small children is higher than for adults, but it is not so generally realized that 30 minims will not affect one adult so much as 10 minims will another. And yet the effect of belladonna is so definite that, as with digitalis, it is essential to ensure that it produces just the effect desired. Some patients need as much as 40 minims three times a day to produce an appreciable effect, a very few are extremely sensitive and suffer from mental effects with as little as 2 minims. Indeed, it is impossible to treat this latter class with belladonna or atropine at all.

The technique is first to give a test dose of 2 minims. This, in an atropine-sensitive patient, will produce a mild disorientation, lasting a short time only but always recognized by the patient. If a larger dose is given, there is a risk of producing serious temporary mania. When it is proved that the patient is not sensitive, start with 10 minims and increase

the dose by 2 minims on each occasion, so that the last dose on the third day will be 26 minims. When the limit is reached, there will be a complaint of dryness in the mouth, difficulty in reading, or flushing after the dose, these are the most common symptoms of poisoning, in that order. Do not tell the patient what to look out for, he will notice it, and complain in due course, and if forewarned will probably imagine symptoms prematurely. In fact, if there is any complaint on a dose of 10 minims, it is best to increase it at once to 15 to make sure, because if it is found to be genuine, it is likely that belladonna treatment is not really indicated. When the limit is reached, cut down the dose by 2 minims, or more, to a convenient figure, and rewrite the prescription to a conventional dose. It can then be given for as long as is necessary.

Belladonna is perfectly safe given in this way, even over long periods. It has no ill-effects, and is a drug of addiction only in the sense that patients are often unwilling to give up what has done them so much good, even when it is no longer necessary. It is usually best to give alkali at the same time. High acidity of the gastric contents contributes to biliary spasm and gall-bladder dyspepsia is often helped by sodium bicarbonate. A good vehicle is tincture of rhubarb and water, it has a very comforting effect on the stomach in many diseases of the liver.

DRUGS ACTING ON THE LIVER CELLS

In cases of parenchymatous liver damage, cholagogues or choleretics have often been used in the past, but it has become understood that there is little point in trying to make a diseased liver secrete bile, and that when bile salts are not being excreted by the liver their administration may be actually deleterious.

THREE VALUABLE REMEDIES

For the treatment of the parenchymatous cells of the liver there are a certain number of drugs of known value, and a large number the efficacy of which is believed in with little or no scientific proof. Easily at the head of the list of valuable drugs comes glucose. This is admittedly a food, and dietetics fall

outside the scope of this article, but it is more than a food to the liver, it is essential to the process of glycuronation besides being the substance from which it derives its energy. However it exerts its remarkable power on the liver, one thing is certain that the liver deprived of glycogen falls an easy prey to any toxic process, and is likely to be affected by the fatty change in the portal zone, associated with ketosis and enforced fat metabolism. It is better to give glucose as such than to rely on the patient's digestion of starchy or sweet foods. It is difficult to give too much, because the patient refuses to take it when he becomes satiated, indeed the art of giving glucose is to present it in palatable forms. Sweets and barley-sugar may suffice for a short time, but their appeal soon wears off and the familiar bottle of barley-sugar by the bedside although academically reassuring, is of little value to the invalid. Glucose-sweetened lemonade, made from fresh lemons, is better, but this should be changed for other fruit drinks before it becomes tiring. It is the lemon taste which the patient comes to dislike; this can be minimized by not putting peel in the lemonade. Grape-fruit or pineapple juices are admirable substitutes; orange juice is not so good because it is sweet enough already, and it is important not to nauseate the patient with sweet things. It is wiser to fall short of the desired amount of glucose than to let a patient "turn against" sweet drinks. If fruit flavours pall, glucose solution slightly acidulated with citric or tartaric acid, freely diluted with soda water, may be tried, the carbon dioxide largely paralyses taste. Glucose should be given in any case of liver disease in which the polygonal cells are or are likely to be, affected and the amount required should be directly proportional to the risk of liver necrosis ("liver atrophy"). *The risk* is the indication, not the fact. Necrosis of the liver is too dangerous to be awaited, it should be prevented. This is not so difficult as it sounds, if it is remembered that almost all diseases of liver cells resemble "delayed chloroform poisoning," in that the clinical evidence of liver necrosis follows the actual damage, after an interval the liver is poisoned first and the patient is poisoned subsequently by the failure of the liver. Even catarrhal jaundice

is a "delayed" liver disease, the damage is done during the prodromal period before the jaundice appears. Give glucose in any case in which the liver is likely, on grounds of clinical experience, to suffer, not forgetting such possible causes as passive venous congestion in heart failure and severe cases of Graves's disease or pneumonia.

Next to glucose comes *calcium*. There is experimental as well as clinical evidence for this. There are two ways of increasing the amount of calcium available for the liver, one is to give it in a form which will be absorbed, the other to mobilize it from the bones by giving acids. Calcium lactate is not sufficiently absorbed to be the perfect form to administer, and acidification is better avoided because the liver works best with a plentiful supply of alkalis. There are two methods of administration—the oral and the parenteral. The oral suffices for the least urgent cases, but the parenteral is the method of choice in emergencies, and has the advantage that it is known that the calcium is arriving where it is needed and in what amount. Orally, calcium sodium lactate is certainly efficient. It is best given in doses of 20 to 60 grains three times a day. Calcium chloride is a gastric irritant, but small doses of 1 to 2 grains in weak solution ($\frac{1}{2}$ to 1 per cent) are usually innocuous. Other forms of calcium may be effective when given by the mouth, but the above are of known efficacy. By injection calcium chloride, 1 per cent in distilled water, may be given with care. It is dangerous to inject it rapidly, as it stops the heart, and twenty minutes should be taken to give the dose of 100 c cm. Calcium gluconate or laevulinate, which may be obtained ready for injection in ampoules (10 c cm), is better, but even this is not fool proof, it is easy to stop the heart by injecting calcium, even in this form if it is done rapidly. A simple safety device is to use a fine hypodermic needle for the intravenous injection. It seems absurd ever to use anything else, except for blood transfusions but there is a common prejudice in favour of "vein puncture needles" for anything to do with veins. Never inject calcium into anything but a vein—it can cause unpleasant necrosis of tissue and, even if the practitioner cannot see the necrosis of an intramuscular injection, the

victim can feel it. If calcium is being given by injection, one dose a day is enough.

The other drug which seems to do good in diseases of the liver cells is *sodium bicarbonate*. Any alkali will do, but this is the natural one and the easiest to obtain. The evidence for its value is not nearly so good as it is for glucose and calcium, but at least there seems to be clinical evidence in its favour. There is no need to make the urine alkaline; 10 grains, three times a day, is enough.

CHAPTER X

THE MODERN TREATMENT OF
INTESTINAL PARASITES

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CHAPTER X

THE MODERN TREATMENT OF INTESTINAL PARASITES

THE treatment of helminthic disease has of necessity become of paramount importance in tropical practice and, as a corollary, new drugs and special methods have been evolved in combating the large number of intestinal parasites abounding in tropical countries and the cause of wide spread disease and death. It may therefore be justly stated that the various forms of helminthiasis claim a larger number of victims than almost any other group of diseases.

The helminths affecting man are divisible into three orders — The trematodes or flukes, the nematodes or roundworms, and the cestodes, or tapeworms. In each of these orders certain drugs are specific and what is lethal to one form has proved to be innocuous to another.

TREMATODES

FASCIOLOPSIS BUSKII is a large trematode which normally lives in the small intestine of man and which resembles *Fasciola hepatica*, the liver fluke. It is found mainly in China, where it produces malaise, slight anaemia and diarrhoea, and in heavy infections, a mild form of hepatic cirrhosis. Fortunately the parasite is easily expelled by several antihelminthic drugs — notably thymol (45 to 60 grains), betanaphthol (3 to 10 grains), carbon tetrachloride (60 minims), or oil of eucalyptus (30 minims), as in ankylostomiasis.

Fasciola hepatica of the sheep is an erratic infestation of the bile and hepatic ducts in man, eventually producing cirrhosis of the liver. Cases have been reported in England, and it may prove to be more common here than is suspected. No specific treatment has been devised although emetine injections (1 grain), for ten days at a course are said to be effective.

CLONORCHIS SINENSIS, the Chinese fluke, inhabits the gall bladder and biliary passages of man in China and eventually produces slowly developing liver cirrhosis. Treatment has so far been unsatisfactory, but recently it has been claimed that gentian violet given by mouth is lethal to this parasite. Unfortunately the dye appears to be toxic for man and therefore great care must be exercised in its administration. Kawai (1937), in experimentally infected dogs, found that 18 mgm of the drug per kgm body-weight administered every three days, was effective. Faust (1939) asserts that in man the dye should be given in enteric coated pills on alternate days in doses not exceeding 30 mgm per dose and the total dosage not in excess of 300 mgm per kgm body-weight—until a total amount of 6 gm (90 grains) of the dye has been given. Gentian violet has also been given intravenously in 40 c cm of a 0.5 per cent solution.

PARAGONIMUS WESTERMANII, the lung fluke of man, is found in Japan and Korea and is widely distributed in carnivorous animals in the tropics and in the United States of America. The treatment has so far been unsatisfactory, although it has been claimed that injections of emetine hydrochloride (1 grain) for ten to twelve injections or intravenous injections of tartar emetic, as in bilharziasis, give temporary relief.

BILHARZIASIS—B HÆMATOBIA, B MANSONI, B JAPONICA—Of the three species of bilharzia parasitic to man the first named is the most amenable to specific treatment. The best method is undoubtedly by intravenous injections of antimony tartrate as originally described by Christopherson in 1917. On account of its lower toxicity, sodium antimony tartrate is the drug of choice for intravenous medication but potassium antimony tartrate (tartar emetic) is somewhat cheaper and more stable in solution. For the average male patient the total dosage necessary to extirpate the parasites is 25 to 30 grains. The initial dose should be $\frac{1}{2}$ grain dissolved in 10 c cm distilled water, and by gradually increasing by $\frac{1}{2}$ grain on alternate days the maximum tolerated dose at 2 to 2½ grains.

is reached. The toxic effects noted after injection are headaches, spasmodic cough, nausea and vomiting, and rheumatic pains in the joints, more especially that of the shoulder. Antimony tartrate treatment is contraindicated in diseases of the heart, liver and kidneys and in hepatic cirrhosis.

Fouadin (neoantumosan) is a trivalent compound of antimony which has been much utilized in the treatment of bilharziasis in Egypt. It has the advantage that it may be given *intramuscularly* without producing grave local disturbance. In some instances in Egypt, however, grave toxic results have been noted. It is given in 7 per cent solution in ampoules ranging from 1.5 to 5 c cm. The total number of injections should be ten to fifteen and a total of 40 c cm is necessary. Emetine hydrochloride has also been found to be therapeutic for bilharzia and is given intravenously in doses of 1 grain up to a total of 20 grains. It is, however, apt to be followed by toxic manifestations, as emetine exerts a definite deleterious effect on cardiac muscle.

NEMATODES

There are several prominent and well-known members of this group —

ASCARIS LUMBRICOIDES inhabits the small intestine, where it may sometimes be found in large numbers coiled together so as to cause intestinal obstruction. In its migrations the worm may wander into other organs, such as the appendix, causing serious inflammation, or into the common bile duct or pancreatic ducts. Minor infestations may produce digestive disturbances and there is generally loss of appetite and, in children, insomnia. The most common complaint is intermittent intestinal colic.

The most widely used drug in the treatment of ascaris is santonin, but it has been recently superseded by others shortly to be mentioned. It is apparently more lethal to the female than to the male, so that several treatments are necessary. It is most active when prescribed with castor oil or calomel as follows —

B	Santonin	-	-	-	-	-	4 grains
	Oil ricini	-	-	-	-	-	180 minims
	Mucil acac	-	-	-	-	-	240 minims
	Syrup	-	-	-	-	-	60 minims
	Aquam menth pip ad	-	-	-	-	-	½ ounce

This should be taken fasting in the morning. An alternative method consists of taking santonin 5 grains, with calomel 2 grains, on three successive nights, followed by a saline purge, such as magnesium sulphate, six hours afterwards. Following the administration of santonin there are usually some ill effects, such as diarrhoea, headache, vertigo, yellow vision, nausea or, in extreme instances, convulsions and coma. Usually the urine is green or yellow when acid, purplish or red when alkaline. Oil of chenopodium (*Chenopodium anthelminticum*) is even more effective and the active principle is *ascaridole* (45 to 70 per cent). It is a potent drug and is extremely irritating to the skin and mucous membrane. Its absorption is rapid and in large doses it causes depression of the respiratory centres. It is therefore contraindicated in cases of cardiac, hepatic, or visual disorders, and definitely so in pregnancy. The drug is put up in hard gelatin capsules, each containing 3 minims (0.177 c cm). The routine dose is 24 minims (1.5 c cm). Eight capsules should be given in two lots of four at a half-hour interval. For children the dose should be 1 minim for each year of age up to sixteen. The drug is best administered three hours after a light meal. A quarter to half an hour after it has been taken a strong saline purge (sod sulph ½ ounce) is given with the object of getting rid of the unabsorbed portion of the drug and of expelling the partly paralysed worms. Carbon tetrachloride (*tetraform*) is a synthetic product allied to chloroform. It is a colourless, volatile liquid and causes a preliminary burning of the mucous membranes which is followed by an anaesthetic effect. When absorbed by the liver it may give rise to delayed toxic symptoms and therefore it should not be administered in cases of alcoholism, cirrhosis of the liver, renal or respiratory disease, or during the course of a fever. The dose for an adult is 60 minims in hard gelatin capsules, each containing 30 minims of carbon tetrachloride.

The minimal dose is 3 minims and it should be increased by that amount for each year of age up to maturity. The drug is best given in the morning on an empty stomach preceded the night before by $\frac{1}{2}$ ounce of sod sulph, and its administration should be followed within half an hour by an equal amount. Trichlor-ethylene is the same in dosage and has a pleasanter taste and odour than carbon tetrachloride. It produces no apparent liver damage. Hexylresorcinol has been employed in the same manner as in ankylostomiasis. Phenothiazine (thiodiphenylamide) is a dye of the methylene blue and thionin group which has recently been employed with great success, especially in veterinary medicine, where it is known as phenovis. I have been engaged recently in testing its anthelmintic properties in man. The conclusion reached (Manson-Bahr, 1940) is that it is effective in human ascaris infection, possibly more so than any other form of treatment. The dosage should be 8 to 10 gm (120 to 150 grains), made up with bile salts in tablet form (Imperial Chemical Industries). The effects are cumulative, and the drug should be administered early in the morning daily for ten consecutive days and then should be followed by a saline aperient. No special preparation of the patient or dietetic precautions are necessary. The worms, which are usually stained red by the dye may be passed *en masse* during the course of the treatment.

(N.B.—It is not as widely recognized as it should be that the dead worms may not be passed for several days subsequent to treatment. At first they may be stupefied, expiring later or may for some reason or another be held up.)

ANKYLOSTOMIASIS ANCYLOSTOMA DUODENALE, and NECATOR AMERICANUS—Hookworm disease constitutes the most serious and wide-spread nematode infection throughout the tropics. These parasites produce a severe anaemia and may cause death in a number of ways. They inhabit the small intestine especially the duodenum and ileum. The characteristic anaemia is microcytic and hypochromic, indicating a severe loss in iron and therefore ferrous salts are indicated in combating this serious feature. Numerous drugs

have been employed from time to time for eradication of the worms

Thymol was originally employed, the dose for an adult male being 60 grains, for a woman 45 grains, for children under five, 8 grains, from five to ten, 15 grains, from ten to fifteen, 30 grains. On account of its toxic properties thymol should not be given more than once a week and then on an empty stomach followed within one hour by a saline aperient, and the patient should have special dietetic preparation one day before treatment. Betanaphthol in doses of from 3 to 10 grains is given in the same manner as thymol, but is apparently less efficacious. Oil of chenopodium has been found to be on the whole more efficacious than either of the foregoing. The dosage is the same as that advocated for ascaris and should be followed within a quarter of an hour by a strong saline purge. A repetition of this form of treatment should be undertaken after a week's interval, not before. Carbon tetrachloride is employed in the same manner as already described, but should be administered with special care, taking into consideration the enfeebled and anaemic condition of the patient. He should be confined to bed for the day of his treatment, and it is important to note that not all the hookworms killed by this treatment are to be found in the first stool, but may continue to appear for three or four days. Naturally the faeces should be washed and sieved to recover the defunct and not easily detectable worms, whereas the eggs continue to be passed in small numbers in the stool for several days after all the worms have been exterminated. Tetrachlorethylene has been advocated in America as being less toxic than the foregoing and is given in exactly the same way, but is apparently not quite so efficacious. *The combined treatment* has shown itself to be more efficient when carbon tetrachloride and oil of chenopodium are combined. The patient should have been suitably prepared for one day and a saline aperient administered the night before and about one hour afterwards. The dose recommended is carbon tetrachloride 40 minims, oil of chenopodium 17 minims, liq. paraffio (excipient) 1 ounce. It is found advantageous to give the mixture in two halves with a quarter of an hour's interval.

Hexylresorcinol (caprokol) is moderately efficient in eradicating hookworms and is also used in threadworm infections. It is given in hard gelatin capsules, or crystoids. It has the advantage of being relatively non-toxic, and can be administered without interfering with the daily routine.

WHIPWORM (TRICHURIS TRICHIURA Syn TRICHOCEPHALUS DISPAR)—The worm, extremely common in most tropical countries, is also found in Great Britain. It lives in the cæcum, often in the vermiform appendix, and occasionally in the lower ileum and is apparently non-pathogenic. A certain number can be dislodged by the carbon tetrachloride and oil of chenopodium mixture. Faust asserts that it has been known in Brazil for a long time that the fresh latex of *Ficus glabrata* (*leche de higueron*) taken on an empty stomach in 2 ounce doses removes the parasites. Unfortunately the principle of the latex cannot be preserved. A proprietary preparation of the crude latex from Colombia is sold in America as "higueronia."

THREADWORM (OXYURIS VERMICULARIS)—This well known pest causes irritative symptoms mainly in children. Although normally inhabitating the upper portion of the large intestine, the gravid females migrate into the rectum to oviposit, and are often found at night outside the anus. It must be admitted that up to the present the treatment of this affection has been unsatisfactory. The worms can be expelled by quassia enemas. After evacuation of the rectum by means of a hot-water enema, an effusion of quassia (1 40) is injected slowly and allowed to percolate throughout the bowel. At the same time quassia used to be given by the mouth in the form of "quassin" tablets, but this treatment is only partially effective and cannot be said, at any time, to have totally exterminated the parasites. It should be emphasized that the gravid females are not difficult to dislodge, and this can be done to some extent by a high soap and water enema, or even 2½ per cent quinoxyl solution (10 ounces), but with the immature and male forms it is a difficult matter, as they cannot be reached in the upper portions of the large intestine. Many other methods

of treatment have been tried from time to time "Butolan" (*p*-benzylphenol carbamin acid ester) (Bayer) given by the mouth in doses of 0.5 gm three times daily for one week appeared to achieve a certain measure of success, especially in small children, but sometimes it appears to have no effect at all. The carbon tetrachloride and oil of chenopodium mixture described on page 122 certainly dislodges a number of the worms but is as a rule too toxic for children. In America hexyl-resorcinol has been widely used, in enteric-coated tablets of 1 gm (15 grains) daily doses for fourteen days or longer, supplemented by high enemas of the same in 0.1 per cent solution (8 to 12 ounces), to be retained for ten to twenty minutes. It is recommended that both rectal and oral treatment should be repeated every three to four weeks. Wright *et al* (1940) in America prefer the gentian-violet medicinal treatment to all others. The dye is administered, as stated on page 118, in enteric-coated tablets daily before meals. The adult dose is 1 grain three times daily, either for sixteen consecutive days, or for two periods of eight days each with a week's rest between. For children the daily dosage recommended is 1 cgm ($\frac{1}{6}$ grain) for each year of age. Some authorities have reported discomfort following administration, including nausea and vomiting.

It is not surprising therefore that as one dye has been found specific for this resistant nematode, phenothiazine (Imperial Chemical Industries) should also prove efficacious. From my experience it seems to be the most easily administered and the most efficient method at present available. In man in contradistinction to what obtains in animals a single maximal therapeutic dose does not suffice to exterminate all the threadworms. Apparently, too, in man the dye has a cumulative action. The dose in tablet form for children from five to ten years of age is 1 gm (15 grains) a day for at least ten consecutive days, below five years 0.5 gm ($\frac{7}{12}$ grains) suffices. A saline aperient should be given at the conclusion of the course and no special dieting is necessary. The tablets are best given in the morning, crushed and concealed conveniently in a sweet or jujube. For adults, especially women, in whom this parasite is often so difficult to dislodge, the dose should be 8 to 12 gm (120 to 180

grains) for the same period. After the fourth day the dead and moribund threadworms can be found in the faeces. Patients should be warned that the urine is invariably stained red, and this begins about half an hour after administration and continues for twenty-four hours.

STRONGYLOIDES STERCORALIS—This small parasitic nematode is chiefly remarkable for its elaborate life history and also for its minute size. It lies buried in the submucous tissue of the small intestine. The active larvae are numerous in the faeces in tropical countries. It is doubtful if it is pathogenic in all cases and at the most it produces a mild form of diarrhoea. Until recently no form of effective treatment had been evolved, but De Langen has shown that gentian violet, as used in the dosage and manner recorded on page 118 is lethal for the parasitic female strongyloides. The total dosage is 48 grains over a period of sixteen days.

CESTODES

The more common human tapeworms are *Tænia saginata* (the beef tapeworm), *T. solium* (pork tapeworm), *Diphyllobothrium latum* (broad or fish tapeworm), and in most tropical countries the dwarf tapeworm, *Hymenolepis nana*. Of these *D. latum* and *T. solium* are the most easy to dislodge. The commonest and most widely spread, *T. saginata*, have proved most difficult to eradicate, although unprovided with hooklets on the rostellum as in *T. solium*.

DIPHYLLOBOTRIUM LATUM lives in the small intestine of man, dog, cat, bear, walrus, sea-lion, fox, mink, pig, and mongoose. It is easily dislodged with filix mas, oleoresin of aspidium, and even carbon tetrachloride. The French, since the time of Davanne (1860), have favoured karmala (the glandular red powder attached to the capsule of *Rottleria tinctoria*). The dose is 12 to 33 gm for an adult and $\frac{1}{2}$ to 1 gm for an infant. The tincture is preferable, the dose being 30 to 23 minims according to age. If the worm has not been expelled within two hours, castor oil should be administered.

TÆNIA SOLIUM is fairly easy to cure with the ordinary filix mas treatment detailed on page 126, as well as with carbon

tetrachloride and oil of chenopodium mixture To obtain fair success in the treatment of *Tenia saginata* infestation it is most necessary to pay attention to details in treatment

Filix mas—The preparation of the patient is essential He should be put to bed and starved for two days, nutriment being reduced to weak tea, a few slices of toast, an unlimited amount of barley water sweetened with glucose, and an aperient, such as laxen, or some preparation of senna, should be given each night In order to clear the bowel of mucus the following mixture should be given on each of the two days —

B Ammon chlor	-	-	-	-	-	15 grains
Tinct limonis	-	-	-	-	-	44 minims
Spir chloroformi				-		10 minims
Aquam ad	-	-	-	-		½ ounce

Early on the morning of the third day, on an empty stomach, extract of *filix mas* (rhizome of the male fern extractum *filicis liquidum*, *Dryopteris*, or *Aspidium marginalis*) should be administered in doses of 60 to 120 minims for an adult male Most practitioners give too small a dose When given in liquid form it may provoke vomiting and is therefore best prescribed in gelatin capsules each containing 15 minims European males can take 120 minims without provoking any undue disturbance and females 60 to 90 minims The method of treatment advocated is —At 8 a m two capsules of 15 minims of *filix mas* are given, they must be swallowed, and further additions at half hour intervals The patient should remain thereafter perfectly quiet, to avoid vomiting and take sips of water sweetened with glucose I prefer to reinforce the treatment an hour later with a mixture of oil of turpentine (30 minims) emulsified with mucilage of acacia At 10 30 a m the saline aperient of sod sulph should be given Then diarrhoea should ensue and a hot-water enema (20 ounces) should be injected Shortly afterwards segments of the worm should appear, and when passed in long ribbons the head should be brought away and easily recognized Sitting on a night commode containing steaming hot water is said to facilitate the passing of the worm When the head has appeared the patient may be permitted a light meal, but no alcohol

In America (Golob, 1935) a few authorities favour transduodenal medication. The argument in favour of this method is that it requires smaller doses of the toxic drug and the action on the parasite is direct. Golob gives the following prescription —

R. Oleoresin of aspidium -	120 minims
Mucilage of acacia -	60 minims
Aquam dest - - -	60 minims
Sat sol mag sulph - - - -	60 minims

The patient is prepared by saline purgation the night before and requires no post-treatment catharsis. The method is contraindicated for the aged, infants under one year, and pregnant women.

The preparation of oleoresin of aspidium (U S P) contains *filicin*, the anhydride of filicic acid. This preparation is favoured in America and is given as follows —

Oleoresin of aspidium - -	60 minims
Pulv acaciae - - - -	30 minims
Aquam dest ad - - - -	1 ounce

The details to be observed are the same as above.

Pelletierine is a mixture of two alkaloids—pelletierine and isopelletierine, obtained from the roots and bark of the pomegranate (*Punica granatum*). The dose is 7 grains dissolved in alcohol followed two hours later by oil ric 1 ounce and a soap-and-water enema. Melon seeds (*Cucurbita maxima*) are much used in the Levant. They should not be more than a month old, and should be deprived of their seed-coats. The dose for an adult is 700 gm (10,500 grains). The seeds are given with honey, and this high dose is swallowed in the morning on an empty stomach followed by a saline aperient. Areca nut (*Areca catechu*) is employed in China. The dose is 30 gm (450 grains) of the powdered nut boiled for thirty minutes with 200 c cm (7 ounces) of water and taken on an empty stomach. The carbon tetrachloride and oil of chenopodium mixture (see p 122) given as in ankylostomiasis is sometimes effective when other measures fail. Kousso, the flowers of *Brayera anthelmintica*, are used to evacuate *T. saginata* by the Ethiopians. It has a very dis-

agreeable taste and is irritating to the intestinal mucosa. Hiyeda and Terada (1939) report favourably in Japan on "raigan" (*Omphalia lapidescens*), a kind of mushroom, in a powdered state in doses of 20 grains three times daily for three days. No preliminary treatment is necessary.

N.B.—It should be emphasized that when once numbers of segments have broken away with any form of treatment and the head still remains in the host, further drug treatment is invariably unsuccessful until the worm has grown to an appreciable length, which is usually after an interval of six weeks or longer. Failure to recognize the importance of this statement may lead the practitioner to repeat *filix mas* treatment at weekly intervals, when by so doing he not only fails to achieve the dislodgement of the worm, but may also cause *filix mas* poisoning, which may result, as has recently happened, in polyneuritis and in blindness, due to paralysis of the iris. Excessive doses of *filix mas* may also produce bilirubinaemia, jaundice, and even, eventually, cirrhosis of the liver.

HYMENOLEPIS NANA is most difficult to dislodge in large numbers (it is usually a multiple infection). Faust recommends oleoresin of aspidium, oil of chenopodium or, hexylresorcinol. Maplestone and Mukerji (1939), however, have recently published a paper praising the gentian-violet treatment which has already been adequately described.

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CHAPTER XI

DIURETICS AND URINARY ANTISEPTICS

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CHAPTER XI

DIURETICS AND URINARY ANTISEPTICS

DIURETICS

DIURESIS is induced by changes affecting the composition of the blood, the renal cells, or the circulation in the kidneys, or more usually by a combination of these factors. Of the diuretics in common use, the *saline group* (urea, citrates, acetates) may be regarded as acting primarily through an alteration in the blood. There is a corresponding change in the glomerular filtrate, which now contains more of a substance (e.g. urea, potassium bicarbonate) not easily reabsorbed by the tubular epithelium. Such a substance, by its osmotic pressure, tends to retain more water in the tubules, and thus the volume of urine is increased. Potassium and sodium citrate and acetate are oxidized, for the most part, to bicarbonates in the body, and so make the urine alkaline. Potassium salts cause more diuresis than sodium salts because the potassium ion is more effectively excreted by the kidneys. Ammonium citrate and acetate, after oxidation to ammonium bicarbonate, are converted into urea, and hence produce little change in the reaction of the urine, although diuresis alone tends to diminish the acidity of the urine by increasing its resemblance to the plasma.

The *caffeine group* of diuretics (caffeine, theobromine, and theophylline) act primarily on the cells of the kidney. They may augment filtration through the glomerular membrane or reduce absorption of water from the tubules.

The *mercurial* diuretics probably cause slight irritation of the kidneys, so that the changes produced will affect the local circulation, although they will not necessarily be confined to this. In fact, all diuretics are likely to accelerate the blood

flow through the kidneys, presumably as a secondary effect in many cases, since in animal experiments diuresis is sometimes observed with unaltered blood flow. In the resting kidney filtration is probably restricted to a relatively small number of glomeruli, although a considerable proportion of functional units are inactive. Diuresis brings more glomeruli and tubules into action, as the blood flow through previously inactive glomeruli is increased.

Drugs of the *digitalis* type (*digitalis*, *strophanthus*, *squill*) are not diuretics in a general sense but, nevertheless, they may cause diuresis in cardiac oedema. They do so by improving the circulation throughout the body. The capillary pressure is probably reduced. Fluid from the tissues then enters the blood and can be excreted by the kidneys. *Squill* is said to cause more diuresis than *digitalis*, and is sometimes credited with a direct action on the kidneys.

In oedematous conditions treatment is usually directed towards diuresis and no change in the reaction of the urine is necessary. The drugs available include two of the saline group, urea and potassium nitrate, the purine diuretics caffeine, theobromine and theophylline, and mercurials, mercury pill, calomel, and organic mercury compounds. When the blood urea is normal, urea is probably the best saline diuretic for general use (240 grains dissolved in 5 ounces of water, flavoured with tincture of orange). It is rapidly absorbed and is almost non toxic. Apparently diuresis is caused by its resistance to reabsorption of water from the renal tubules. The resulting concentration of the blood favours the passage of fluid from the tissues to the circulation. Urea is, however, very diffusible, and soon reaches about as high a concentration in the oedema fluid as in the blood so that its power of drawing water from the tissues is probably limited. A further disadvantage is that its nauseating properties make frequent administration impossible. Potassium nitrate acts in much the same way as urea, with perhaps more power of direct withdrawal of water from the tissues. It may cause some gastric disturbance and occasionally slight irritation of the kidneys. It has been superseded to a great extent by urea.

Less frequently employed saline diuretics deserve some mention in connexion with the treatment of anuria rather than oedema. All the *saline purgatives* would have a diuretic action if they were absorbed sufficiently from the intestine. Two of them can be used parenterally to induce diuresis. These are sodium sulphate and magnesium sulphate, and they are generally given by intravenous injection. Neither of these drugs diffuses into the tissues as readily as urea and they are both more effectively excreted by the kidneys. They are therefore powerful diuretics. Sodium sulphate has little toxicity and seems to deserve a wider field of application. Magnesium sulphate is a powerful depressant of the central nervous system. Thus its parenteral use should be restricted to convulsive states in which this action, as well as the diuresis, is of value. The heart is depressed also and the treatment is not free from danger. Careful attention must be paid to dosage, and a solution of calcium chloride or gluconate, which antagonizes magnesium, should be ready for injection if needed.

Uræmia is an important emergency demanding rapid diuresis. Uræmia complicating acute glomerulo nephritis responds promptly to intravenous injection of a solution of sodium sulphate or glucose. These remedies are likewise indicated in the urinary suppression which supervenes after operations on the genito-urinary tract, and in the latent uræmia of urinary obstruction, after the obstruction has been dealt with. Incidentally, they alleviate the cerebral irritative manifestations commonly found in uræmic states by lowering intracranial tension.

The most useful solutions are —

4 to 8 per cent sodium sulphate (cryst) For a child of six years 10 ounces for an adult, one pint

2 per cent magnesium sulphate, 1 c cm per kgm body weight
20 per cent glucose dosage similar to sodium sulphate

Sucrose (10 ounces of 20 per cent solution intravenously) has theoretically much to commend it and has been used extensively in America. Unfortunately this substance is liable to provoke unpleasant reactions.

The *purine* diuretics are often disappointing. This is prob-

ably because most patients have acquired tolerance by drinking tea coffee or cocoa. Theophylline is the most powerful diuretic of the three but it is more likely than the others to cause digestive disturbance. Theobromine is a slightly better diuretic than caffeine. Both theophylline and caffeine have a stimulant action on the central nervous system and may cause insomnia. This action is almost absent in theobromine. The pharmacopœial preparations of these drugs are designed to increase their solubility rather than to modify their action. Theophyll et sod acet is given in doses of 2 to 5 grains and theobrom et sod salicyl has a dosage of 10 to 20 grains. The unofficial drug aminophylline (euphyllin 1½ to 3 grains) is theophylline with ethylenediamine added to accelerate its effect by making it more soluble. Theophylline monoethanolamine (theaminin Lilly) has been found remarkably active against cardiac dropsy. It is supplied in 3 grain capsules and in ampoules for injection. The contents of an intravenous ampoule may be usefully added to a hypertonic glucose infusion.

THE MERCURIAL DIURETICS

Some diuresis may be obtained by oral administration of *inorganic mercury* in suitable forms e.g. pil hydrarg calomel but its irritant action is exerted in the alimentary canal as well as on the kidneys and purgation may limit the diuresis. Its diuretic effect is in any case not likely to be great since only small amounts are absorbed. The organic mercury compounds however are among the most useful diuretics available and often succeed when other remedies fail. The earliest was the proprietary drug novasurol which has been superseded by more recent compounds. These include the pharmacopœial mersalyl corresponding to the proprietary salyrgan and two other proprietary drugs novunt (chinoin) already well known and esidrone (Ciba) which has recently been introduced (Uhlmann 1938 Hartmann and Panizzon 1938). There is probably little to choose between these drugs provided that they are supplemented by theophylline if they do not already contain it.

DeGraff, Battermann, and Lehman (1938a) found that the local toxic effects of intramuscular injection are almost prevented by theophylline, and (1938b) that the rate of absorption from the tissues is much increased. Thus 97 per cent of the drug was absorbed in an hour, or three times more than when given alone. The rate of excretion was also greater, partly because of more rapid absorption, but partly also for other reasons, since a 30 to 40 per cent increase occurred even with intravenous injection (DeGraff *et al.*, 1938). Typical examples of this combination are injectio mersalyli (B P Addendum, dose 8 to 30 minims), novunt (chinoïn), esidrone (Ciba), mersalyli (British Drug Houses), and mersalyli (Burroughs Wellcome & Co.). The dose may be given into a vein, or preferably deeply into a muscle. The diuretic effect is enhanced by administration of ammonium chloride orally (30 grains three or four times daily), for a day or two before each injection. Frequency of dosage depends upon the individual response. The first dose should be a trial one of $\frac{1}{2}$ to 1 c cm, if no untoward manifestations occur 1 to 2 c cm may be given at intervals of three days. Once drainage is tolerably good, a weekly or fortnightly injection may suffice. These drugs are also available in tablet and suppository form, but their activity is comparatively slight, and the suppositories have been known to cause rectal irritation. They may merit trial as maintenance routine in patients who are averse to injections.

The mercurial diuretics are potent against all types of anasarca, provided that renal function is moderately good, in non-renal oedema with intact kidney function their action is often dramatic. They sometimes cause undesirable effects, such as increase of albuminuria, haematuria, and cast formation, diarrhoea, and an increase in the non-protein nitrogen of the blood. Even damaged kidneys seem fairly tolerant of the mercurial diuretics, and their dangers have possibly been overestimated.

DIET AND OTHER MEASURES

The oedema of nephrosis is often more difficult of dispersal than cardiac oedema, because loss of albumin causes failure of

the plasma proteins to retain water in the circulation. Epstein (1917) emphasized this aspect of the mechanism of oedema, and suggested the use of diets rich in protein but poor in fat and carbohydrate. In all nephritis, except early acute cases or those having a high level of blood urea, a liberal and well-mixed diet rich in protein is essential to compensate for renal leakage. Salt must be eliminated as far as possible from the diet, and the fluid intake limited to two pints daily. In addition to increasing the serum albumin, the excess of urea from a high protein diet acts as a diuretic. Many nephritics suffer from hypochromic anaemia, and this should be corrected by liberal dosage of iron.

Nephrotic subjects sometimes show a low basal metabolic rate (-10 to -25 per cent), and Fahr (1937) points out three possible factors in this connexion —

- (1) The low B.M.R. may be apparent, the body-weight being fallacious as it includes the weight of oedema fluid.
- (2) Chronic starvation caused by misguided dietetic restrictions.
- (3) Thyroglobulin is probably filtered out of the blood plasma by the damaged kidneys.

Blood transfusion would seem an appropriate method of remedying plasma deficiencies, but in practice the benefit is transitory. The use of concentrated blood serum is a recent development. Aldrich *et al* (1938) treated a small series of lipid nephrotics with intravenous doses of human blood serum which had been concentrated fivefold by vacuum dehydration. They report immediate diuresis and apparent regression of the nephrosis. *Acacia solutions* by the intravenous route have been advocated for the treatment of massive dropsy, but their use is not free from risk. Goudsmit's (1937) routine for this drug is —

Give 9 gm. potassium nitrate daily in $\frac{1}{2}$ gm. capsules.
Restrict fluid to 1 to $1\frac{1}{2}$ pints daily.
Salt free diet containing 100 gm. protein and having a calorie value of 2,000.

Give sufficient thyroid extract (5 to 10 grains daily) to raise the B.M.R. to +5 to +10 per cent

Give 350 to 500 c.cm. of 6 per cent acacia in normal saline intravenously Repeat

Follow with injections of mersalyl

Other writers use acacia in concentrations up to 30 per cent, and this would seem more rational

DIURESIS IN NON-RENAL CONDITIONS

Cardiac dropsy is a fruitful field for the administration of diuretics. In most cases of cardiac failure there is an element of renal inadequacy. A preliminary assessment of kidney function should be made, including urine examination and blood-urea estimation. Gross kidney damage contraindicates the use of mercurial diuretics, otherwise they are conspicuously successful in cardiac oedema. Mersalyl or novunt should be given freely at the outset, and the action must be reinforced by that of the classical cardiac tonics digitalis and strophanthus. Massive cardiac dropsy must be treated energetically, and all other measures of dehydration exploited, e.g. an initial purge, acupuncture of the lower limbs and aspiration of transudates from the pleurae and peritoneum. Once oedema-free a maintenance dose of digitalis, combined with an occasional injection of mersalyl or theamin, will often suffice to keep the patient comfortable. Guy's pill (pulv. digitalis, pulv. scillae, and pil. hydrarg. 1 grain) is an excellent combination for maintenance purposes, and is one of the few traditional remedies with a formula consonant with modern pharmacological principles.

Diuretics, particularly the mercurials, are serviceable for prevention of recurrence of transudates in serous cavities, such as ascites from portal obstruction polyserositis, non inflammatory pleural effusions. Migraine occasionally responds to intravenous injections of mersalyl, and this dehydration therapy is also useful in labyrinthitis and Ménière's syndrome. An adequate supply of vitamins should be ensured in all cases of cardiac and renal oedema. There is some evidence that injections of an active vitamin B₁ preparation heighten the efficacy of diuretic therapy, especially in cardiac insufficiency.

CHANGING THE REACTION OF THE URINE

At the usual reactions, normal urine contains a mixture of monobasic phosphate (acid sodium phosphate for the most part) and dibasic phosphate (chiefly sodium phosphate). In an alkaline urine the phosphate may all be in the dibasic form, and bicarbonate may be present as well. In an extremely acid urine all the phosphate may (rarely) be monobasic. The urine can be made alkaline by giving sodium or potassium bicarbonate, or, better, by giving salts which interfere less with gastric digestion but are oxidized to bicarbonate after they have been absorbed. In general, this oxidation occurs in the case of organic salts of the methane series, whereas those of the benzene series are not broken down in the body. Thus sodium acetate and sodium citrate act as alkalis but not sodium salicylate, or sodium mandelate. Alkalies are of great utility in oliguria, particularly that associated with febrile states. In acute glomerulo-nephritis alkaline salts have found great favour, as they encourage the re-establishment of urinary excretion.

To make the urine acid is sometimes a difficult matter, because organisms may be present which break down urea to form ammonium bicarbonate, and this must be neutralized before an acid reaction can be obtained. Hence the great advantage of urinary antiseptics which are effective in an alkaline medium.

By giving acid sodium phosphate the urine can be made acid in the most natural way. But phosphate is badly absorbed from the intestine, sodium phosphate (the dibasic form) is, in fact, sometimes used as a saline purgative, and owes its effect to the difficulty in its absorption. The acid salt may be slightly better absorbed.

More artificial methods of making the urine acid are often more effective. These depend on reducing the alkali reserve of the body, so that the kidneys will retain as much alkali as they can. If an ammonium salt of some acid not oxidized in the body (e.g. ammonium chloride, nitrate, mandelate) is given, this salt may be considered as reacting with the sodium bicarbonate of the plasma to form ammonium bicarbonate and

the sodium salt of the acid. The ammonium bicarbonate is converted into urea, and the result is loss of sodium bicarbonate from the body. The same result may be obtained in another way. If calcium chloride or mandelate is given, a very small part of the calcium is absorbed from the intestine. But the calcium salt can react in the intestine with sodium bicarbonate, so that calcium carbonate or bicarbonate may be left, and sodium chloride or sodium mandelate is absorbed. Thus some sodium bicarbonate is lost which would ordinarily have been reabsorbed from the intestine. These considerations show why ammonium mandelate and calcium mandelate have been introduced to avoid the use of ammonium chloride or calcium chloride which would be necessary if sodium mandelate were employed.

In the course of any therapy for which an acid urine is essential for efficient action of the chosen antiseptic, the pH of the urine must be tested frequently and the dose of acidifying salt adjusted accordingly. A universal indicator may be used or, better still, an indicator covering the appropriate range of reaction, e.g. methyl red.

URINARY ANTISEPTICS

An antiseptic action in the urinary tract can be obtained in a manner not possible in any other route by which waste products are excreted (e.g. lungs, skin). This is because the kidneys can concentrate suitable antiseptics, so that a toxic concentration in the blood is not needed to provide a bacteriostatic action in the urine. With the *sulphonamide* drugs the great advance in treatment of certain infections depends on the fact that an antiseptic concentration can be attained even in the blood and tissues. It might be hoped therefore that no further concentration by the kidneys would be necessary for urinary antisepsis. At present such optimism is not altogether justified by clinical experience although when the concentrating power is unsatisfactory successful results are more frequent with these drugs than with any others. The field of action of the sulphonamides is wider in the urine than in the blood. Species of organisms unaffected by the concentration in the blood

may be destroyed by the higher concentration in the urine, and greater numbers of bacteria per c cm. can be controlled.

Recent improvements in the treatment of urinary infections have rendered obsolete most of the older antiseptics. Hexamine was one of the best of these, and is still sometimes used. It is inactive in the blood and tissues, but in acid urine some of it is decomposed and formaldehyde is liberated. Decomposition must occur in the stomach also, and the drug is probably best given before meals, although if less formaldehyde is then produced it has more chance of irritating the empty stomach. Dunlop (1937) was uncertain of any beneficial effects of hexamine in either acute or chronic cases, and could get no evidence of activity *in vitro* when testing the acidified urine of patients to whom the drug had been given. Acid sodium phosphate was formerly in vogue as an acidifier with hexamine, but its unreliability in this connexion has already been mentioned. Ammonium chloride or nitrate is more satisfactory. Calcium chloride, although not so active, has the merit of greater palatability. A suitable urinary pH for hexamine treatment is about 6 (yellow to universal indicator, orange to methyl red).

R	Hexamin	-	10-20 grains
	Tinct aurant	-	10 minims
	Aquam ad -	-	½ ounce
	q i d a c		
R	Ammon chlorid	-	10-20 grains
	Ext glycyrrh. liq	-	10 minims
	Aquam ad -	-	½ ounce
	q i d p c		

Hexamine is sometimes helpful in the chronic recurrent pyelitis common in elderly visceroptotic females. Cases of this kind should first be cleared with a more active antiseptic. Afterwards, courses of hexamine even if not successful in maintaining sterility of the urine, will often keep the patient free from symptoms. The relation between bowel irregularity and urinary sepsis must be borne in mind and an attempt made to secure regular evacuation without catharsis. This may call for dietary adjustment, bowel lubrication, suitable exercise, abdominal massage, or the wearing of an abdominal

support. Many advertised remedies for obesity contain purgatives and indeed purgatives form the basis of most widely advertised nostrums. Pyektis in an otherwise healthy young adult demands inquiry as to possible patent medicine addiction.

Adair, Dunlop, and Willmert (1938) have examined the action of *pyridium*. They find that in the concentrations attainable in the urine *pyridium* has little germicidal power either at acid or alkaline reactions. No evidence could be obtained that it reduces the virulence of organisms or the toxicity of toxins. It inhibits the production of staphylococcal haemolysin and necrotizing toxin, and although these bodies were not found in the urine of patients with untreated staphylococcal infections of the urinary tract, the authors consider that the beneficial effects of *pyridium* in such infections may be thus explained. There is a distinct inhibitory effect on the growth of haemolytic streptococci, but not of *B. coli*.

Two other dye compounds have lately been used with success. These are *benzochrome* (Decker and Texone 1938) and *phenothiazone* (DeEds, Stockton, and Thomas 1939). The latter drug succeeded in one case after mandelic acid and sulphanilamide had failed, but more work must be done before its value can be assessed.

THE KETOGENIC DIET AND MANDELIC ACID

Within the past decade the first considerable advance in treatment of urinary infections was the introduction of the *ketogenic diet*. Clark (1931) and Helmholtz (1931) reported that the urine of epileptic patients undergoing ketogenic diet treatment was bacteriostatic. The bacteriostatic substance was identified by Fuller (1933) as β hydroxybutyric acid, and the urine was invariably acid in reaction. Thus, induced ketosis quickly found a wide field of therapeutic application. On a more natural diet the body destroys β hydroxybutyric acid and hence this substance fails as an alternative to dietetic treatment. Acids which contain the benzene ring are less easily broken down, and Rosenheim (1935) suggested mandelic acid as an effective substitute.

Mandelic acid, however given, cannot exist as an acid in the blood. It is therefore used as a neutral salt, which is less irritant to the alimentary canal, and the urine is acidified by other methods. The effectiveness of a given concentration of mandelic acid in the urine depends upon the acidity. The more acid the urine, the greater the disinfectant action. Some bacteria are more easily killed than others. Most observers find *B. coli* less resistant than staphylococci (Carroll, Lewis and Kappel, 1938a, Cook, 1938, Droller, 1938 and others), but Helmholz (1938-39) states that the effect on *Staphylococcus aureus* is almost the same as on Gram-negative bacilli. *B. proteus* is fairly resistant even if the urine can be made acid, this is often difficult because the organism breaks down urea to ammonia. Enterococcal infections may respond to mandelic acid.

No serious consequences are likely to result from treatment with this drug, and in animal experiments transient pathological changes only are induced (Carroll, Lewis and Kappel, 1938a and b, McMahon 1939). Many patients, however, suffer from nausea and vomiting and in some the treatment must be discontinued. These symptoms are probably caused by the salt action in the stomach of mandelate preparations and of acidifying agents, if these are given separately. The action is usually much less severe when the insoluble calcium mandelate is used, and this compound seems to be almost as effective as the ammonium salt (Melton and Rosenheim, 1938, Droller, 1938). Rupel and Travis (1939) have succeeded in treating intolerant patients with tablets containing monoethanolamine mandelate and ammonium chloride, protected with a special enteric coating (Lilly). Other unpleasant effects are occasional tinnitus, headache, and skin reactions, microscopic haematuria or hyaline casts in the urine and, rarely, gross haematuria (Cook, 1937).

There is not complete agreement about the urinary concentration of mandelic acid which clinicians may expect to attain. Possibly methods of estimation are at fault. McMahon (1939) found that in patients who were given 12 gm of mandelic acid per day the concentration in twenty four hours was

0.5 per cent. or less. The highest excretion was obtained with enteric coated tablets, and the lowest with calcium mandelate. He points out that 0.5 per cent. would be optimum only with high acidity of the urine. Carroll, Lewis, and Kappel (1938a) state that a dosage of 3 gm. four-hourly gives a concentration of 1 per cent. for six hours in a patient with a urinary output of 1,200 c.cm., and Helmholtz (1938-39) believes that this concentration can be maintained. Randall and Hughes (1938) recommend limitation of fluid intake in acute infections to about 1,500 c.cm daily. Braasch (see Cook, 1937) rightly emphasizes that mandelates and acidifying agents are contraindicated in renal insufficiency, not only because of possible irritation of the kidneys but also because a bactericidal concentration cannot be achieved.

Diet.—Although the ketogenic diet has been supplanted by mandelate therapy, it is occasionally useful in conjunction with mandelate in cases in which difficulty is experienced in obtaining a sufficiently acid urine, particularly when acidifying salts are badly tolerated. The following diet yields an acid residue and is adaptable to individual taste:—

BREAKFAST.—Tomato juice. Oatmeal porridge and cream. Fried or scrambled egg; fat bacon or fish. Tea with cream and saccharine.

DINNER.—Meat, fish, chicken or savoury omelette. 3 per cent. vegetables (cabbage, cauliflower, spinach, celery, broccoli, leeks, onions). Salad, mayonnaise or oil dressing. Oatcakes, butter, and cheese. Cocoa with cream and saccharine.

TEA.—Egg or sardine sandwiches. Thin slices of bread, liberally buttered, or hot buttered tea cake. Tea with cream and saccharine.

SUPPER.—Boiled ham (fat) or fish (herring, mackerel, cod, salmon, or salmon trout). 3 per cent. vegetables. Oatcakes or ryvita, with butter and cheese. Nuts. Coffee with cream and saccharine.

Ammonium mandelate, introduced by Holling and Platt (1936), is the most commonly used salt. Some ammonium chloride may be needed to maintain the urinary pH at 5.4. This should be checked twice daily by adding a few drops of methyl red to an inch of urine in a test tube. A rose-pink

colour indicates the requisite acidity, yellow-pink or orange means that the dose of ammonium chloride must be increased

R	Ammon mandelat	-	-	-	-	1 ounce
	Ext glycyrrh liq					
	Syr ää	-	-	-	-	20 minims
	Aquam chlorof ad	-	-	-	-	2 ounces
For a child of 1 year	-	-	-	q.i.d	30 minims	
" " 5 years	-	-	-	t.i.d	60 minims	
" " 10 "	-	-	-	q.i.d	90 minims	
For an adult	-	-	-	q.i.d	120 minims	
						Ex aq
R	Ammon chlorid	-	-	-	-	2 ounces
	Tinct aurant	-	-	-	-	80 minims
	Inf gent co ad	-	-	-	-	8 ounces
For a child	-	-	-	q.i.d	60-120 minims	
For an adult	-	-	-	q.i.d	½-1 ounce	
						Ex aq

Calcium mandelate, suggested by Schnohr (1937), is also efficient, it is insoluble in water and tasteless, although more acidifier is sometimes necessary

The urinary concentration of mandelate should be kept, if possible, at 1 per cent, and dosage calculation may be made on this figure. If the output of urine approaches 1,000 c cm daily, the necessary dose of mandelic acid would be 10 gm, or about 180 grains, for a daily excretion of two pints. A child passing a pint of urine daily needs 90 grains of mandelate. In practice these doses should be regarded as minimal. The following amounts of various mandelate preparations represent the approximate equivalents of 3 gm of mandelic acid —

Sodium mandelate	-	-	-	3 4 gm
Neoket (Boots)	-	-	-	90 grains
Ammonium mandelate	-	-	-	3 3 gm
Ammoket (Boots)	-	-	-	½ ounce
Mandelix (B D H)	-	-	-	120 minims
Calcnum mandelate	-	-	-	3 5 gm
Mandecal (B D H)	-	-	-	70 grains

Mandelate treatment should be given for eight to fourteen days, if a sterile urine is not obtained, the course may be repeated after a fortnight's interval. Rest in bed and warmth

are important in acute cases of urinary infection, irrespective of the antiseptic used

THE SULPHONAMIDES

The second advance in treatment followed the introduction of the sulphonamides. Their powers are less limited in the urinary tract than in the tissues, since the concentration is higher in the urine than in the blood. At the same time, the unique bacteriostatic effect of sulphonamides at blood concentrations renders them superior to all earlier urinary antiseptics when the kidneys are inefficient (Helmholz, 1938-39) or the prostate is involved (Buchtel and Cook, 1937, Cook 1938, Crenshaw and Cook, 1939). The simplest of these drugs is sulphanilamide, which appears as effective as any of the others, except in gonorrhœal conditions. It acts best in alkaline urine (Helmholz and Osterberg, 1937, Randall and Hughes 1938) and is active on *B. proteus* and similar urea splitting organisms. It is not successful in enterococcal infections, for which mandelic acid or intravenous neoarsphenamine (Cook, 1938) should be used. *Staphylococci* are not all equally susceptible. Helmholz (1937) found that one strain was destroyed, and in two others the growth was reduced, whereas Cook (1938) has had better results in bacillary than in coccal infections (see also Crenshaw and Cook, 1939). All agree that *B. coli* is susceptible, but mixed infections may be difficult to treat (Vest, Hill and Colston (1939)).

The effective concentration in the urine varies between 25 and 40 mgm per cent (Helmholz and Osterberg, 1937, Melton and Beck, 1939) depending on the reaction (Helmholz and Osterberg, 1937), and on the number and nature of the organisms (Vest, Hill, and Colston 1939). Concentrations of 12 to 20 mgm per cent have been claimed in the prostatic secretion (Buchtel and Cook, 1937), but most writers have found less there than in the blood. The lower estimates are more credible since glands not concerned with excretion are unlikely to concentrate anything but their own specific products. At any rate, even low concentrations are probably of therapeutic value.

Sulphanilamide gives brilliant results in urinary infections, in dosage considerably smaller than that required in the more aggressive septicæmic states. The ingestion of reasonable quantities of fluid does not seem to mitigate the beneficial action of the drug, provided that adequate urinary concentration is obtained.

The following is a representative dosage scheme —

Infant, 1 gm daily

Child of six years 2 gm daily

Adult, 4-6 gm daily

Injections should be resorted to only if gastric intolerance contraindicates oral dosage. It is difficult to obtain sufficient urinary concentration with parenteral treatment.

Children tolerate sulphanilamide well, and relatively large doses have been given to infants. Summerfeldt and Mitchell (1939) warn against limitation of fluid. This may be useful in adults but in children dehydration and acidosis can easily occur. The higher relative dosage compensates for the amount of fluid allowed, and acidosis is avoided by giving an equal amount of sodium bicarbonate.

Sulphapyridine (M & B 693) has also been tried in urinary infections with results similar to those given by sulphanilamide, but further experience must accumulate before definite conclusions can be reached. Melton and Beck (1939) find that the bactericidal action of this drug is obtained at lower concentrations, and is less influenced by urinary reaction. Thus, although 15 mgm per cent of sulphapyridine was effective in acid or alkaline urine 30 mgm per cent of sulphanilamide had an equal effect only when the urine was alkaline. A resistant strain of *B. coli* was inhibited more by sulphapyridine, even in the presence of albuminuria.

Secondary reactions — During treatment with any of the sulphonamide drugs the patient must be kept under close observation. Malaise, headache, and nausea are common, but do not necessitate discontinuance of the drug, whereas according to Crenshaw and Cook (1939) general illness, fever, and vomiting do. Cyanosis is observed in a considerable number of

cases, and sometimes methaemoglobin and sulphæmoglobin can be detected in the blood. These changes are thought to be favoured by the presence of unoxidized or partially oxidized sulphur, so that articles of diet containing sulphur should be excluded. Sodium and magnesium sulphate are often regarded as harmful. In sulphates, however, the sulphur is fully oxidized. The sulphate ion is chemically stable almost inert in the body, and unlikely to increase the toxicity of sulphanilamide. The harmful effects of these salts should be attributed to purgation, and purgatives of all kinds should be avoided. Less attention is now paid to cyanosis than formerly, but Crenshaw and Cook still regard it as a possible forerunner of haemolytic anaemia and agranulocytosis and they think that these disasters can be prevented by giving cyanosis the respect it deserves.

Two types of skin reaction are described. One is localized to exposed parts of the skin and is probably caused by increased sensitivity to light. Treatment is stopped temporarily, but may be resumed later if the patient is warned to avoid sunlight. The other skin reaction affects the whole body. It is a toxic dermatitis of the morbilliform type, and its recurrence precludes further use of the drug (Crenshaw and Cook, 1939). Giddiness and visual disturbances have been reported. Gastric disturbance appears to be more frequent, and cyanosis less frequent, with sulphapyridine than with sulphanilamide. Nausea and vomiting seem to be reduced by giving 15 grains of sodium bicarbonate and 90 minims of glucose in an ounce of water fifteen minutes before sulphapyridine. Grinding the tablets in milk makes them more easily retained.

Given by mouth, these drugs reach therapeutic concentrations of about 25 to 60 mgm per cent (free) in the blood, and 25 to 60 mgm per cent (free) in the urine. Sulphapyridine is less soluble than sulphanilamide, and absorption is more difficult and less regular. Attainable concentrations of sulphapyridine are therefore sometimes below the ranges stated but may nevertheless be effective. Both drugs are partially detoxicated in the body by the formation of acetyl derivatives, which are found in the blood and excreted in the urine along with the unaltered drug. The amount of conjugation varies greatly, and

the acetyl compounds seem to have no bacteriostatic action (Helmholz and Osterberg, 1937)

The relative merits of mandelate and sulphonamide therapy may be summarized briefly in the following statement — Both are efficient and may be relied upon to cure 70 to 80 per cent of cases of urinary tract infection after eight to fourteen days' treatment. Mandelate is irritant to the stomach and urinary acidification is at times a troublesome detail. From the important view point of the patient's comfort sulphanilamide is therefore the drug of choice but unfortunately, its toxic effects are more likely to be serious. Mandelate is more expensive, a representative proprietary preparation costing 12s 6d for a week's supply, exclusive of acidifier and indicator, as compared with sulphanilamide at 2s 6d. Details of the individual case will often provide a clear indication for treatment. For example a patient whose renal function is so impaired as to interfere with concentration of mandelate and acid will be more likely to improve on sulphanilamide, which acts at a lower concentration. Again the presence of prostatic enlargement and infection are indications for sulphanilamide. The type of infecting organism sometimes governs the choice of treatment. Infections with *B. coli* and its variants *B. lactis aerogenes*, and most streptococci are amenable to either drug. Sulphanilamide is ineffective in enterococcal infections, but fortunately this organism responds well to mandelate treatment. *B. pyocyanus* and *B. proteus* infections require sulphanilamide. Staphylococcal infections do not yield satisfactorily to mandelate, and many cases are disappointing with sulphanilamide. Here uleron (four half gramme tablets daily for six days) or sulphapyridine may be substituted. Immunization with staphylococcal toxin is also worth a trial. Sulphathiazole, a recent addition to the sulphonamide group, is claimed to be a more powerful anti-staphylococcal agent than the others and this has lately been confirmed by Helmholz (1940) as far as urinary disinfection is concerned. Crystallization of the insoluble acetyl derivative of this drug in the urinary tract is a possible source of trouble, but can apparently be avoided by keeping the urine alkaline. Cases of mixed infection, e.g. *B. coli* and enterococci are not

rare, and the complementary actions of the two drugs may be utilized by giving a course of sulphanilamide and afterwards one of mandelate

Cases which are resistant to treatment, or those which relapse, call for complete investigation of the conformation and function of the genito urinary system. The difficulties attendant on poor renal function have already been considered. Patients with renal obstruction, as by stone or enlarged prostate, are prone to relapse unless the underlying condition is treated surgically. A course of sulphonamide therapy covering the immediate pre- and post-operative period will lessen materially the operative risk. Failure in children almost always means the presence of congenital abnormality of the urinary system, and this should be sought by cystoscopy and pyelography.

Pyelitis of pregnancy is likely to be obstinate on account of the obstructive element of ureteric compression by the gravid uterus. Sulphanilamide is well tolerated, and is often successful, whereas mandelate aggravates the hyperemetic tendency. Patients showing symptoms of ureteric obstruction such as severe renal pain, rigors, vomiting, and fever, should be nursed in the prone position with the middle section of the mattress removed. If this is unsuccessful, continuous ureteric catheterization after the method of Dix and Evans (1939) may be instituted.

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CHAPTER XII

STIMULANT DRUGS

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CHAPTER XII

STIMULANT DRUGS

THE clinical uses of drugs which stimulate the central nervous system are chiefly symptomatic and palliative. The treatment of schizophrenia (Meduna, 1935) and related depressive states by induced cardiazol convulsions is almost the only example of the curative use of a stimulant drug. Stimulants are widely used for their action on the medullary centres in circulatory failure, acute respiratory disease, asphyxia of the newly born or drowning, deep anaesthesia associated with respiratory arrest, and also as antidotes in narcotic poisoning.

The investigation of antidotes to poisoning with barbiturates and other substances used to procure basal anaesthesia has drawn attention to a group of analeptic drugs. The name analeptic, using the word in the opposite sense to cataleptic, suggests a drug which possesses awakening properties, by virtue of its stimulant action on the cerebral cortex, e.g. picrotoxin and cardiazol. The analeptic group is commonly extended to include drugs which have, in addition, a powerful stimulant action on the respiration and circulation, and beneficial cardiac effects. Analetics are often used to counteract circulatory shock.

MECHANISM OF DEPRESSION

Shock, or collapse, may develop rapidly as a result of trauma or haemorrhage, or in the course of acute infections, sepsis or intoxication. It is characterized by ashen grey pallor, impaired mental acuity, cold perspiration, shallow respiration, a thready pulse, and a fall in blood pressure. The condition is usually associated with disordered peripheral circulation rather than with any intrinsic defect in the heart or in the central nervous control. The capillaries are dilated and engorged and their walls become increasingly permeable. Exuded fluid stagnates

in the capillary bed, thus decreasing the venous return to the heart and the volume of blood in active circulation. As the blood pressure falls in developing shock the sympathetic centre, which is regulated by the pressure in the carotid sinus, is stimulated, the heart works to the maximum of its ability and the arterioles contract. Under these conditions the value of a drug cannot depend upon its power to stimulate either the circulatory centres or the heart itself. As the circulation fails, inadequate coronary flow causes inadequate oxygen supply to the heart, cardiac output falls, and the compensatory mechanisms are impaired by the resulting medullary anaemia. Anaemia of the respiratory centre completes the vicious circle by further depleting the oxygen supply to the heart and brain. The efficacy of any drug used to break this vicious circle probably depends primarily on the stimulant action which the drug exerts upon the respiratory centre. All stimulant drugs in common use (some of which are described briefly in the following paragraphs) are capable of stimulating the respiratory centre and producing secondary beneficial cardiac effects and therefore all possess some degree of analeptic action. Ephedrine and benzedrine, which dilate the coronary vessels by peripheral sympathetic stimulation in addition to stimulating the medulla, may prove to be particularly valuable analeptics for use in circulatory disorders.

DRUGS AND PREPARATIONS

CAFFEINE stimulates the entire central nervous system as a beverage it is used for its cortical action, therapeutically as a medullary stimulant, and in toxic doses it increases spinal activity. Its action, unlike that of most stimulants, is not followed by a phase of depression, hence its safe use in poisoning with opium or alcohol. Caffeine facilitates the transmission of impulses through the conductile muscle of the heart, which may add to its value in the treatment of circulatory failure.

Caffeina et sodii benzoas (B.P.) 2 to 5 grains subcutaneously

STRYCHNINE stimulates the nervous system more powerfully than caffeine, and has a singularly marked action on the

spinal cord. Acute poisoning is characterized by tetanic convulsions of spinal origin. In clinical doses strychnine increases reflex response and muscle tone, but its reputation as a "tonic," when given orally, largely depends on the improvement in appetite caused by its bitter taste, and on increased intestinal movement due to a direct action on the gut. Strychnine is a powerful respiratory stimulant and therefore a valuable analeptic, although it has no direct action on the heart. Coughing and expectoration may be increased owing to exaggerated reflex response and increased tone in the chest muscles.

Injectio strychninae (B.P.C.) 5 to 10 minims subcutaneously (about 1/30 to 1/15 grain strychnine hydrochloride)

CAMPHOR potentially causes convulsions, which are clonic in type and of cortical origin, thus resembling all the common convulsant drugs, with the exception of strychnine. Camphor stimulates the medullary centres, but its insolubility and slow absorption detract from its usefulness for this purpose, neither does experimental investigation of its cardiac actions lend support to the belief that it acts clinically as a direct cardiac stimulant. Local sensory irritation at the site of injection may stimulate the medullary centres reflexly. Such an action would be comparable to that evoked by injection of *spiritus aetheris*, or by *spiritus ammoniae aromaticus* or brandy in contact with the gastric mucosa.

Injectio camphorae (B.P.C.) 1 to 10 in olive oil, 8 to 30 minims subcutaneously

CARDIAZOL (*leptazol, metrazol*), pentamethylenetetrazol, is a white powder, soluble in water. Its actions resemble those of camphor, but are more potent and certain, due to its ready absorption. Induced cardiazol convulsions, of an epileptiform type, are used in the treatment of schizophrenia. Experimental evidence (Werner and Tatum, 1939) shows that cardiazol has a higher safety factor than picrotoxin or coramine when used for this purpose, but Tooth and Blackburn (1939) have drawn attention to the risk of memory impairment after convulsive treatment. Cardiazol and picrotoxin are the two most effective anti-anæsthetic drugs. They shorten the sleeping

time and the recovery period in experimentally induced narcotic poisoning (Barlow, 1935, and Hjort *et al.*, 1938). Cardiazol is a powerful respiratory stimulant and exerts a typical analeptic action when used in shock or in acute respiratory disease associated with circulatory failure. In the heart-lung preparation it has no influence on the heart tone or the coronary flow, and it is probably rendered less effective in the presence of organic heart disease.

Non-official, supplied by Knoll, London, $\frac{1}{4}$ grains in tablets for oral administration in ampoules for hypodermic or intravenous injection (repeat in thirty to sixty minutes if necessary). Ampoules with a three times bigger dose, for use in grave cases of narcotic poisoning to be administered by slow intravenous or intramuscular injection until the patient wakes.

CORAMINE (*nikethamide*), pyridine- β -carbonic acid diethyl amide, is a yellowish liquid, miscible with water. It resembles cardiazol in its cortical convulsant action, but is less potent. Coramine is not used to induce convulsions *per se*, nor is it as effective as cardiazol for waking patients from narcosis. Coramine is a less rapid and potent medullary stimulant than cardiazol, but qualitatively the drugs are similar in their action and use on the medullary centres. In the heart-lung preparation coramine, unlike cardiazol, increases the coronary flow, an action which may add to its value in acute heart failure.

Non official supplied by Ciba London, in 25 per cent solution, 15 to 30 minims orally. Ampoules (1 c.c.m.) for hypodermic or intravenous injection (add to continuous intravenous saline drip in treatment of shock).

PICROTOXIN is a crystalline substance prepared from the seed of *Cocculus indicus*. It induces clonic convulsions and is a powerful medullary stimulant. Experimental results suggest that picrotoxin will prove to be one of the most valuable antidotes in severe grades of poisoning by barbiturates or other narcotics.

Picrotoxin (B.P.C.) 1/100 to 1/25 grain

EPHEDRINE, the chief alkaloid of the Chinese plant, Ma-Huang, is used as a stimulant of the central nervous system.

in the treatment of narcolepsy Ephedrine is also an efficient analeptic in the treatment of circulatory disorders, as its central action is reinforced by peripheral effects characteristic of sympathetic stimulation It inhibits the breakdown of adrenaline in the body, thus causing general vasoconstriction, increased coronary flow, and acceleration and augmentation of the heart beat Ephedrine is of value in the treatment of cardiac syncope attributable to intrinsic disorder of the beat, but should be avoided, because of its action on the heart, in shock due to coronary thrombosis

Ephedrine hydrochloridum (B.P.) $\frac{1}{4}$ to $\frac{1}{2}$ grains orally or hypodermically

BENZEDRINE has a characteristic stimulant action upon the higher psychic centres A clinical dose, taken by a normal person, leads to increased self confidence, lessened fatigue, good humour, talkativeness and sleeplessness Benzedrine is of paramount value in the treatment of narcolepsy, but its relative merit as an antidote in narcotic poisoning is still uncertain Benzedrine has a peripheral sympathetic action similar to that of ephedrine

Non-official, supplied by Menley and James London
Benzedrine sulphate 5 mgm in tablets

LOBELINE (Curtis and Wright, 1926) is an alkaloid which specifically stimulates the respiratory centre by lowering the threshold of its response to carbon dioxide Carbon dioxide itself, 5 to 10 per cent, is the natural and most effective respiratory stimulant Lobeline and carbon dioxide are used in the treatment of respiratory failure, e.g. asphyxia of the new-born, carbon monoxide poisoning, respiratory arrest during anaesthesia The peripheral actions of Lobeline resemble those of nicotine, and it is contraindicated in myocardial disease as it depresses the heart

Non official *Lobeline hydrochloride*, maximum dose $\frac{1}{2}$ grain $\frac{1}{4}$ grain intravenously in 1 per cent solution

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CHAPTER XIII

SEDATIVES AND ANALGESICS

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CHAPTER XIII

SEDATIVES AND ANALGESICS

PAIN, whether of acute, subacute, or discomfort type, affords for its relief many problems to the practitioner. The treatment of continuous or intermittent acute pain, recently described for injuries by Balme (1938, 1939) and for certain surgical conditions by Dodd (1938), presents, as a rule, fewer difficulties than the relief of subacute or mild pain, which, although real to a sensitive patient, gives to the physician little evidence of mental distress.

Pain must be regarded as one of the special senses. Its perception is dependent upon irritation or injury of special peripheral receptors or "end organs," impulses from which are conveyed through sensory nerves and particular spinal tracts to an area adjacent to the lateral nucleus of the thalamus. Here, the pain is first perceived consciously, but the recognition at the thalamic level is of gross changes of pain and temperature. Exact discrimination and analysis of the sensation as to locality, area, relative intensity and character, occur in the sensory cortex, where also originate the anxiety and distress which pain arouses. Pain is physiologically a protective sensation, which may evoke reflexly either the withdrawal of the part from the irritant or, when appropriate, the immobilization of the irritated area. Pain may, however, be pathological, for example, when slight pain, or even a normal stimulus, is aggravated by a facilitated conduction, or a hypersensitive perception, into a severe pain.

It is clear from this summary that the positions at which the sensation of pain can be mitigated or abolished are four — (1) The peripheral receptor (cutaneous or deep), (2) the conducting paths (nerves or spinal cord), (3) the thalamic per-

ceptive centre, and (4) the cortical appreciative centre. The medical terms for pain-relieving drugs—sedatives, analgesics, anodynes, obtundents, and anaesthetics—convey no pharmacological meaning unless qualified by adjectives—local, spinal, central, or general—as in the case of anaesthetics.

This section considers the relative merits of the measures which are of value to relieve pain of varying types and origins, but does not enter into discussion of indirect anodynes, such as the value of iodides in syphilitic periostitis, salicylates in acute rheumatism, or purgatives in colic.

SUPERFICIAL ANODYNES, ANALGESICS, OR OBTDUNENTS

Two physiological principles lend support to the accepted clinical value of local sensory stimulants or "counter irritants" in relieving pain arising from the peripheral receptors, namely, (1) that the impulses from the new sensory stimulus or "pain" will occupy entirely the conducting paths and also the attention of the sensory cortex, to the exclusion of the former perception or consciousness of pain. This also explains the relief of "referred" pain by cutaneous irritants applied to the painful area, and (2) that a constant slight stimulus to sensory endings induces fatigue of the irritability or 'depression' of the receptors.

Into this category falls the use of heat in the forms of the india-rubber hot-water bottle, the crushed linseed poultice, or the more expensive cataplasma kaolini co., the last has the advantage that the volatile oils—thymol methyl salicylate, and peppermint—which it contains—prolong the analgesic effect of the heat, a similar action is achieved by the mustard poultice or turpentine stupe.

The pharmacopoeial liniments afford ample choice of rubefacient anodynes for the relief of pain from sprains, myalgia, lumbago, and fibrositis, their local vasodilator effect and the subjective sensation of warmth contribute to the relief they afford. For more localized application, for instance to small neuralgic areas, more concentrated, saponaceous or fatty preparations of volatile oils are better, such as the menthol

and wintergreen creams or ointments. Liquor iodi mutis is also serviceable. The superficial anodyne action of volatile oils, e.g. clove oil, thymol, is applied in dentistry for the relief of pain from sensitive dentine or from an exposed pulp.

LOCAL ANÆSTHETICS

The employment of the local anæsthetics—cocaine, procaine, percaïne, for surgical and other purposes, has recently been described by Romanis (1938). In general, as a surface anæsthetic for mucous membranes, cocaine hydrochloride still retains its superiority, owing to its easy absorption. Hence it is incorporated (usually $1/20$ grain) in antiseptic pastilles and lozenges for painful tonsillitis and pharyngitis, and in suppositories ($\frac{1}{4}$ grain) for painful haemorrhoids. Cocaine has been supplanted for interstitial injection, regional and spinal anæsthesia, by procaine and others, which rarely cause toxic symptoms. Benzocaine (anæsthesin) and orthocaine (orthoform), being sparingly soluble in water, are useful anæsthetic dusting powders for burns, ulcers, pruritus and itching skin diseases, owing to their slow solution, their analgesic action persists, and benzocaine (10 per cent in an ointment basis or suppository) affords relief for several hours in anal fissure and piles. Quinine and urea hydrochloride (2 per cent) has been used as an anodyne antiseptic for wounds, its analgesic effect is less, but much more prolonged than that of cocaine, unfortunately, it delays the healing of wounds and its use should be restricted to temporary application to painful surface wounds or burns.

THALAMIC DEPRESSANTS—ANALGESIC ANTIPYRETICS

The central antipyretics lower febrile temperature by influencing the heat regulating centre in the corpus striatum so as to lower the point of thermal equilibrium, their power of relieving pain is due to a similar depressant action on the thalamic cell station on the path of the pain fibres. These drugs can relieve pain—often of a considerable degree—without interfering with the intellectual functions of the cerebrum,

although by relieving pain, they often act indirectly as soporifics. Their anodyne action is most successful for the relief of headache, neuralgia, migraine, referred pain, sciatica and fibrositis, and pain from dental caries or pulpitis, but they also are worthy of trial, before resorting to morphine, in pain arising from wounds, fractures, tabes, acute gout, and even carcinoma. The important drugs in this group are acetylsalicylic acid, phenacetin, acetanilide, phenazone and amidopyrine. Of these, acetylsalicylic acid and phenacetin (acetophenetidin) are relatively innocuous although, in sensitive persons, the former may cause facial urticaria and oedema, and the latter erythematous rashes and, more rarely, owing to slow formation of para aminophenol, methaemoglobinæmia with symptoms of cyanosis, cardiac weakness and breathlessness. Calcium acetylsalicylate, more soluble than the acid, acts a little more rapidly, and the potency of phenacetin is said to be increased by prescribing with it half its weight of magnesium oxide. Acetanilide (antifebrin), which undergoes decomposition into para-aminophenol more rapidly than phenacetin, is rarely used now because of the frequency of toxic effects.

Phenazone (antipyrin) being freely soluble, acts rapidly although for less time, because it is quickly excreted. It does not cause methaemoglobin formation but not uncommonly produces skin rashes and circulatory collapse. Amidopyrine (pyramidon), although a better analgesic than the others, is liable to produce severe agranulocytosis and caution should be observed in its use. An unwelcome feature of the action of analgesic antipyretics is their proclivity to cause sweating.

Commonly, phenacetin, phenazone or acetylsalicylic acid, as an analgesic, is prescribed along with caffeine citrate (1 grain) in powder or tablet form, the combination is effective, particularly for headaches and neuralgias, but the cerebral stimulant action of caffeine may retard sleep—the substitution of theobromine for it in some proprietary tablets is not logical.

Many proprietary analgesic preparations consist simply of mixtures in therapeutic doses of compounds of these drugs with an hypnotic, usually a barbiturate. Amidopyrine is a frequent basis and its presence is not always apparent from

the proprietary name. The following is a representative, but incomplete list of such preparations.

DRUG	DOSE	COMPOSITION
Sonalgin	1 tablet	Phenacetin 3½ grains, butobarbitone 1½ grains
Veganin	1-2 tablets	Phenacetin 3½ grains, acetylsalicylic ac. 3½ grains, codeine 1/10 grain
Migraine	8-15 grains	Phenazone and caffeine citrate
Novalgin	5-15 ..	Phenazone, sodium methyl-amino-methane sulphonate of.
Veramon	1-2 tablets	Amidopyridine, 1 mol, with barbitone, 1 mol (6 grains)
Cibalgin	1-4 ..	Amidopyrine 3½ grains, allobarbitone ½ grain
Amidophen	1-2 capsules	Amidopyrine 3½ grains, phenacetin 1 grain, caffeine ½ grain, hyoscyamus extr. ½ grain
Allonal	1-2 tablets	Amidopyrine 1½ grains with allyl isopropyl barbitone 1 grain
Veropyron	1-2 ..	Amidopyrine 5½ grains, barbitone 2½ grains
Compral	1-2 ..	Amidopyrine with trichlor ethyl urethane (7½ grains)
Gardan	1-2 ..	Amidopyrine with " novalgin " (5 grains)
Trigemus	4-8 grains	Amidopyrine with butyl-chloral hydrate
Asciatine	4-8 ..	Amidopyrine with butyl-chloral hydrate
Somnosal	1-2 tablets	Amidopyrine 2½ grains, brom isovalerenyl urea 5 grains

For details of other similar proprietaries see Extra Pharmacopœia I, 1936; II, 1938; and "A Prescriber's List," Roberts & Co., 76 New Bond Street, W.I. 6th Edition. 1938 (which gives prices).

Such combinations are easily prescribed as powders or tablets, the choice and dosage of analgesic and hypnotic being varied to suit the requirements of individual patients; for convenience, there is available the tabellæ barbitoni et amidopyrinæ (B.P.C.), dose 1 tablet, which contains barbitone 2 grains, and amidopyrine, 4 grains. To show the comparison in prices, the B.P.C. tablets cost 3s per hundred, whereas two near proprietary relatives cost 7s 6d and 10s. 6d. per hundred. None of the salts or derivatives of phenazone or amidopyrine has exhibited any real therapeutic advantages over the parent substances.

CORTICAL SEDATIVES AND ANALGESICS: CENTRAL ANODYNES

It should be recollected that there are pharmacological differences between the progressive actions of the organic hypnotics (and the general anaesthetics) and the more specific

cerebral and medullary actions of morphine. General anaesthetics, including alcohol, and most organic hypnotics, depress the central nervous system in the reverse order of its evolution i.e. progressively, the intellectual, perceptive, sensory and motor cortex, the spinal cord and, finally, the medulla, so that, by selection of a suitable dosage, these drugs may be employed as simple hypnotics, or may be given in amounts sufficient to allay pain by the depression of the sensory cortex and probably also of the thalamus. It is, however, important to remember that the dosage which will alleviate pain is, as a rule, not far short of that capable of causing depression of the medullary centre of respiration.

Morphine, on the other hand, has a selective action on the pain centres and can relieve pain without necessarily inducing sleep, although cerebration is retarded and respiration is slowed, even by small doses.

The drugs regarded as hypnotics do not, in therapeutic dosage, relieve painful impressions but, by depression of the cortical perceptive areas, so minimize or eliminate those external impressions upon which consciousness depends that sleep ensues, the depression necessary to induce sleep does not need to be deep, if the ordinary means—the darkened quiet room and comfortable temperature—are taken to reduce stimuli from the peripheral receptors. The problem in insomnia is more frequently to induce sleep less frequently, to maintain it for the former purpose a short-acting hypnotic is often adequate, for the latter, one of those which have a prolonged effect may be required.

Varying degrees of cortical depression can be achieved by the use of bromides, alcohol, paraldehyde, chloral hydrate and the barbiturates. Except in the case of the bromides, the cerebral actions of these drugs are similar and apart from considerations of prescribing and side actions, there is less problem in selecting a suitable hypnotic than in learning by experience the appropriate dosage for individual cases and in choosing, according to its time of action, the most favourable time for its administration. Many practitioners confine themselves to one or two hypnotics which they have learned

to use with satisfaction and success, others discouraged by failure to achieve uniform results after trying many, encourage the search for new drugs in an already over stocked field.

Bromides depress selectively the intellectual and motor areas, hence they are of particular value as sedatives in states of mental or motor excitement but their actual hypnotic power is relatively weak. Although there is reason to doubt if the bromine ion in complex organic hypnotics plays any important part in their action, it is true that the initial excitement which may precede sleep, when induced by an organic hypnotic can be reduced or avoided by the previous administration of sodium bromide. It is recognized now that no advantage is gained by using mixtures of the three bromides—sodium potassium and ammonium.

The utility of alcohol in mild insomnia is well known. Paraldehyde—as a draught with 16 parts of cinnamon water flavoured with tincture of orange—acts in fifteen minutes and provides a natural sleep of about eight hours duration without after effects, other than the odour of the drug which is excreted in the breath, paraldehyde is safe for cardiac and respiratory diseases. Chloralformamide and chlorbutol (chloretone) are less reliable and slower in action than chloral hydrate, they are, however, both safe and useful in insomnia of cardiac or nervous origin and chlorbutol which is a local anaesthetic in the stomach, often prevents or alleviates sea sickness. Chloral hydrate when prescribed in dilute solution flavoured with orange, acts within thirty minutes and is a reliable general hypnotic, the risk of its depressing cardiac muscle is overrated, but it is not ideal since habit is easily acquired and fatty degeneration of the liver is a sequel of its frequent use.

Carbromal (adakal) is a mild hypnotic which acts usually within half an hour and produces no after effects, it is effective in inducing sleep but this may not last more than four or six hours. Being almost tasteless, carbromal is prescribed (10 grains) as powders or tablets in preference to paraldehyde or chloral, in insomnia arising from mental anxiety, restlessness and cardiac disease.

Sulphonal and methylsulphonal (trional) are not used as routine hypnotics because of their slow absorption, which makes the time for their administration somewhat difficult to estimate, and because of their slow excretion, which causes drowsiness and lethargy on the next day, but in the treatment of mental cases this "hang-over" has its value.

The derivatives of barbituric acid or malonylurea vary in their hypnotic action according to their stability and rate of excretion. Those which are most easily destroyed and rapidly excreted have a brief intensive action. Hexobarbitone soluble (evipan sodium), 40 to 150 minims of a 10 per cent aqueous solution, or pentothal sodium (sodium ethyl methyl butyl-thiobarbiturate), 7 to 15 grains in 5 per cent aqueous solution, can be used as intravenous general anaesthetic agents. Hexobarbitone, 4 to 8 grains given orally, initiates in ten minutes sleep which passes into natural sleep. Others less rapidly detoxicated are used prior to general anaesthetics as basal narcotics, their effective action lasts from four to six hours. Pernocton, 45 minims of a 10 per cent solution and pentobarbitone, 3 to 5 grains in 150 minims of sterile water may be given intravenously, or pentobarbitone $\frac{1}{2}$ to 3 grains amyta $\frac{1}{2}$ grain per lb body-weight, sodium amyta $\frac{1}{2}$ grain per lb body-weight are more usually given by rectal injection although they may be given orally—pentobarbitone $\frac{1}{2}$ to 3 grains, amyta $\frac{1}{2}$ to 5 grains and sodium amyta 1 to 3 grains. Those which are more stable and less rapidly excreted are satisfactory hypnotics and sedatives, namely, barbitone, phenobarbitone, phenitone, allobarbitone, phanodorm and butobarbitone.

All barbiturates are depressants of the respiratory centre and their margins of safety, as represented by the fraction minimal lethal dose therapeutic dose are important. This figure is for evipan 5, allobarbitone 2.5, pentobarbitone, butobarbitone, amyta and phanodorm 2.4, pernocton 2.1, barbitone 1.6 and phenobarbitone 1.27, hence the last may be unsafe in hypnotic doses whereas it is relatively safe in the smaller dosage used as a sedative in epilepsy. The statement that barbiturates do not relieve pain is erroneous, their utility for this purpose depends

on dosage and relative safety. As has been shown, they may be suitably combined with analgesic antipyretics to potentiate their pain relieving properties. With regard to duration of action, this may be judged from the average length of the stupor they cause in rats, namely pentobarbitone 4 hours, pernocton 5 hours, amyntal 6-20 hours, phenobarbitone, allobarbitone, butobarbitone 20 hours, and barbitone 20-30 hours, generally speaking, clinical experience confirms this sequence.

Many practitioners do not realize the close chemical relationship of the barbiturates owing to their appearance under proprietary names. The following list shows their relationship and common synonyms. The symbol BA represents barbituric acid (sometimes called malonylurea) the formula of which is



CONSTITUTION OF BARBITURATES

Rutonal	Phenyl methyl BA	$\text{C}_6\text{H}_5\text{CH}_3$ > BA
Evipan sodium		$\text{C}_6\text{H}_5\text{CH}_2\text{CH}_3$ > BA-CH ₃
Barbitone (veronal)	Di-ethyl BA	$(\text{C}_2\text{H}_5)_2$ > BA
Sod. salt = soluble barbitone (medinal)		
Butobarbitone (soneryl, neonal, soporifene)	Butyl-ethyl BA	$\text{C}_4\text{H}_9\text{C}_2\text{H}_5$ > BA
Pento-barbitone (semtubal)	Sodium salt of iso-methyl-butyl-ethyl BA	$\text{C}_4\text{H}_9(\text{CH}_3)\text{C}_2\text{H}_5$ > BA
Amyntal (sodium salt = amyntal soluble)	Iso-amiyl-ethyl BA	$\text{C}_4\text{H}_9\text{C}_2\text{H}_5$ > BA
Phenobarbitone (fuminal, garidel)	Phenyl-ethyl BA	$\text{C}_6\text{H}_5\text{C}_2\text{H}_5$ > BA
Phenacetone (prominal)	Is methyl phenyl-ethyl BA	$\text{C}_6\text{H}_5\text{CH}_2\text{C}_2\text{H}_5$ > BA-CH ₃
Phanodorm	Cyclohexenyl-ethyl BA	$\text{C}_6\text{H}_5\text{C}_2\text{H}_5$ > BA
Hebaral	Sodium salt of hexyl-ethyl BA	$\text{C}_6\text{H}_{11}\text{C}_2\text{H}_5$ > BA
Allobarbitone (dial)	D-allyl BA	$[\text{CH}_3]_2\text{C}_2\text{H}_5$ > BA
Allonal a compound of amadopyrin with	Isopropyl allyl BA	$\text{C}_3\text{H}_7\text{C}_2\text{H}_5$ > BA
Proponal	Di-propyl BA	$(\text{C}_2\text{H}_5)_2$ > BA
Pernocton	Sodium salt of bromallyl butyl BA	$\text{C}_6\text{H}_5\text{Br-C}_2\text{H}_5$ > BA

Barbitone and its sodium salt (soluble barbitone) act within half an hour, do not influence the digestive, cardiovascular, respiratory, or renal system, and are easily taken in tablet form, hence they have largely displaced other hypnotics for securing sound sleep of about eight hours' duration in the insomnia of neurasthenia, fevers, and cardiac diseases and as a sedative in thyrotoxicosis and chorea. Barbitone is, however, excreted slowly, and therefore some drowsiness or lethargy during the day after its administration is common.

Allobarbitone (dial), $\frac{1}{2}$ to 3 grains, and butobarbitone (soneryl, neonal), 1 to 2 grains, act like barbitone but have

a slightly wider margin of safety and are less liable to cause lassitude on the following day, the latter possesses more decisive analgesic properties than other barbiturates used as sedative hypnotics.

The soluble sodium amyta, 1 to 3 grains, acts more rapidly than amyta, 1½ to 5 grains, both have a less lengthy soporific influence than barbitone and rarely produce any after effects. Similarly, phenodorm 3 to 6 grains, and hebaral sodium, 3 to 6 grains, act rapidly but, being excreted more quickly, are also less lasting soporifics than barbitone. Pentobarbitone (nembutal) 1½ to 3 grains, acts rapidly but for a brief period, its main value is as a basal hypnotic, but pentobarbitone 3 grains, with chloral hydrate 30 grains dissolved in lemonade, is a useful sedative and analgesic during the latter part of the first stage of labour.

Proponal, 2 to 8 grains and somnifaine—a solution of salts of barbituric and allylpropyl barbituric acids—8 to 16 minims are powerful sedatives and hypnotics suitable chiefly for mental cases or to control convulsions in eclampsia, status epilepticus, or tetanus. In urgent circumstances these convulsive conditions can also be treated by the intravenous administration of pentobarbitone or sodium amyta.

It is insufficiently realized that the average hypnotic doses of these drugs, e.g. barbitone 8 grains, phenobarbitone 1 grain, is about four times greater than the sedative dosage which may be repeated at four-hourly intervals.

Phenobarbitone (luminal, gardenal) and its soluble and more rapidly acting sodium salt, differ from other barbiturates in that they are less satisfactory hypnotics but maintain a good and—being slowly excreted—prolonged sedative action upon the motor, and to a less extent upon the sensory cortex. They are therefore efficient means of allaying excitement and restlessness in thyrotoxicosis and of reducing the frequency and severity of the fits in epilepsy without materially impairing the patient's intellect or reflexes as do bromides. Phenobarbitone is of service also to relieve migraine and neuralgic pains. In full doses phenobarbitone is also used to diminish spasms and convulsions in eclampsia, status epilepticus, tetanus,

and strychnine poisoning, soluble phenobarbitone may be given by hypodermic injection in such cases

Phemitone (prominal) 1 to 2 grains, thrice daily, is even more satisfactory than phenobarbitone in severe cases of epilepsy, in which it controls the major fits with less drowsiness and mental impairment. Rutonal, 3 grains is at present on trial for the treatment of epilepsy.

Epanutin (solantoin) sodium diphenyl hydantoinate $1\frac{1}{2}$ to 6 grains, is a feeble hypnotic but a good depressant of the motor area. It is used as a sedative in epilepsy, sometimes in combination with phenobarbitone as a hypnotic. Toxic effects are skin rashes, gingivitis, ptosis and mental confusion.

MORPHINE AND ITS ALLIES

Opium and its chief alkaloid, morphine, are cerebral sedatives and analgesics of the highest value if used in appropriate cases, as means of relieving or mitigating severe pain they are far superior to the analgesic antipyretics or organic hypnotics. The most satisfactory results are achieved from morphine in pain of a constant or recurring type, even under its influence acute exacerbations of pain although ameliorated, are appreciated. It is also when pain is the disturbing cause that morphine is most successful as a sedative and hypnotic.

In acute abdominal disease morphine should be avoided or used only in small doses until diagnosis is certain, unless the nervous collapse and shock subsequent on the severe pain render it essential for the patient's relief. It will effectively relieve the pain—but also obscure the symptoms—of strangulated hernia, intestinal obstruction, appendicitis, renal and biliary colic. The pain of severe injury, fractures, acute gout, and the later stages of carcinoma, usually justifies the use of morphine.

The distressing pain of coronary occlusion can be alleviated by morphine, and the dose may be increased above the pharmacopoeial limit provided a watch is kept upon the respiration, morphine does not impair the cardiac functions in any way, hence, apart from the risk of inducing habit, there is no reason to withhold it as a means of relieving

apprehension and pain and of promoting sleep in cardiac diseases

There is no doubt that morphine has been abused in the treatment of lobar pneumonia. If it is realized that it is a depressant of the respiratory centre in the medulla then the justification for its use depends mainly on the state of that centre. In early stages to relieve pleuritic pain and to ensure by rest and sleep the conservation of the patient's resources it is valuable but it is obviously dangerous in later stages when the respiratory centre is fatigued. Its use as a depressant of the related cough centre should be reserved for cases in which the sputum is scanty but coughing painful or preventing sleep.

The method of administering morphine has become increasingly by the hypodermic syringe this is justifiable when its immediate action is desirable but for most patients oral administration is preferable and there is no reason why instead of the unpleasant tincture of opium morphine hydrochloride in solution should not be given by mouth or the hypodermic tablet be dissolved in water at the bedside and given by this route. Many physicians prefer papaveretum (B.P.C.) (omnopon, alopon, opioidine, pavopin)—a mixture of the hydrochlorides of the opium alkaloids—for oral administrations in doses of $1/6$ to $1/3$ grain in sleeplessness due to pain.

Relatives and derivatives of morphine have been explored to find analgesic substitutes which will produce neither constipation nor habit. There are two groups of these—

(1) *The analgesics resembling morphine.* Papaverine hydrochloride 2 to 4 grains is a weak central analgesic and is employed rather to relax spasm of plain muscle—intestinal, bronchial or ureteral—and to lower blood pressure. It is useless clinically as a substitute for morphine although it does not cause habit. Dihydromorphinone hydrochloride (dilaudid) orally $1/12$ grain hypodermically $1/32$ grain is about ten times more active—hence its small dose—as an analgesic and respiratory depressant than morphine. It has

with truth been advised as a more potent and lasting means of relieving intense pain than morphine but its risks are higher. Both tolerance and addiction have followed its use. Dihydrocodeinone acid tartrate (dicodid) orally 1/13 grain relieves less severe pain and is less toxic than dilaudid but it is really more effective for treating cough. Dihydroxy codeinone hydrochloride (eukodal) orally 1/12 grain is somewhat more toxic than morphine over which it has no advantage (Myers 1933).

(2) *The respiratory and cough depressants* Diamorphine (heroin) methylmorphine (codeine) ethylmorphine (dionin) and benzylmorphine (pernonin) have much less powers to relieve pain than morphine but relatively greater depressant action on the respiratory and cough centres. They are therefore clinically more useful in bronchitis, pulmonary emphysema and whooping-cough but especially with diamorphine their effect upon the respiratory rate should be watched. They are less constipating than morphine. Combinations of these alkaloids with barbiturates in order to enhance their analgesic powers have been prepared e.g. ethylmorphine di allyl barbiturate (dionin + dial) but such combinations when therapeutically necessary can be achieved by prescribing mixtures of either morphine or codeine with a suitable barbiturate.

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CHAPTER XIV

ANTIPYRETICS

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CHAPTER XIV

ANTIPYRETICS

ALTHOUGH it was noted from the earliest times that in many states of disease the patient felt sensations of heat or that his skin was hot to the touch, it was not until about 1870 that exact records of his body temperature began to be kept as a routine. Before the invention of the thermometer this would of course have been impossible, and after thermometers had been made available for general purposes they were still too slow and cumbersome to find their way into general medical use, although the work of Currie (1797) shows that he, at least, was aware of their value.

‘A careful attention’ he says ‘to the changes of the animal heat, and to the state of those functions on which it depends and by which it is regulated, though more requisite in febrile diseases, perhaps, than in others, is however, of importance throughout the whole circle of diseases’.

The subject, however, was largely neglected until the publication in 1868 by Wunderlich of his work ‘Das Verhalten der Eigenwärme in Krankheiten,’ in which were incorporated temperature charts in various types of disease. This work, and the review of it published in 1870 by Clifford Allbutt, drew the attention of the medical world to the importance of temperature changes which have ever since been regarded as one of the most important diagnostic signs. Allbutt at the same time described a modified thermometer which was sufficiently small to carry in the pocket, and accurate enough for the purpose, and which is essentially the same as the clinical thermometer of to-day, except that the recording of the maximum temperature reached was achieved by the inclusion of an air bubble in the mercury column instead of by the constricted stem now in use.

When it became realized that a very large number of morbid

states were accompanied by an increase of body temperature, it was inevitable that search should be made for methods of treatment which were followed by a fall in that temperature, since this seemed to mean a recovery from the disease. Wunderlich noticed that a fall of temperature could be induced by bleeding or by the application of cold to the skin, and he adds that the same result follows "the ingestion of a number of medicines," including calomel, tartar emetic, lead, digitalis, veratrine, quinine, acids, and saline laxatives and emetics. Out of this varied list *quinine* is the only substance that is recognized as antipyretic to-day, and the effects of the others on body temperature are probably due to circulatory depression. It is rather curious that he makes no mention of alcohol, although its effect was certainly known at the time. From then onwards the synthesis of organic compounds and their investigation was continued on an increasing scale, and in 1875 the antipyretic action of the *salicylates* was discovered. A few years later the same property was found in *phenol* and *resorcin*, although these were too toxic for therapeutic use, and in 1884 the first drug manufactured for purely antipyretic use was put on the market under the name of *antipyrin*.

Since then a very large number of compounds have been synthesized with this object, but before describing their action it is necessary to consider the mechanism which maintains the body temperature within fixed limits, whether in health or disease. Those limits, in a healthy adult man, are about 97.5° - 99° F., the variations taking place according to the time of day and the site at which the temperature is measured. The maximum is usually found between 5 and 7 p.m. in day workers. This constancy is of course dependent on the maintenance of an exact balance between heat production and heat loss.

HEAT PRODUCTION AND HEAT LOSS

Heat is produced mainly by the contraction of the body muscles, either in carrying out work or in the maintenance of tone. Minor sources of heat are the metabolism of food materials in the liver and the katabolism of the tissue cells in general. Heat is lost chiefly from the skin, by dilatation of

the skin vessels and evaporation of sweat. A slight loss occurs through the respiratory tract, faeces and urine.

It has been known for a long time that the maintenance of the balance between production and loss is a function of the nervous system. It was formerly thought that the effective mechanism was located in the corpus striatum, but this view was abandoned when it was discovered that removal of this region of the cerebrum did not abolish the power of heat regulation although it did to some extent limit the range within which regulation was possible so that such an animal was less able to withstand extremes of temperature. When, however, the whole of the fore-brain is removed the animal becomes 'cold-blooded' or poikilothermic and takes the temperature of its environment.

It is now generally agreed that the region of the brain which is responsible for maintaining constancy of temperature is some part of the hypothalamus probably in the neighbourhood of the tuber cinereum, although its activities may be modified to some extent by nervous influences from higher parts of the brain. In this connexion it is noteworthy that the regulation of temperature is particularly sensitive to overdosage of drugs of the barbiturate group, which are known to act mainly on the thalamic region. One effect of barbiturate poisoning is to render the organism 'cold blooded'. There is evidence that this centre or mechanism which regulates the temperature of the blood, is acted on by influences of two kinds. One set consists of afferent impulses coming from the cutaneous nerves, the more superficial end-organs reacting to external cold and the deeper ones reacting to rise of internal temperature. These nervous influences are part of a rapid mechanism. The other set is constituted by changes in the temperature of the blood which flows through the nervous system itself. The response to these is usually slower.

The reaction to cooling is twofold. Heat is conserved by contraction of the cutaneous vessels and more heat is produced. This increased production is brought about chiefly by contractions of the voluntary muscles, these contractions being either continuous, as increased tone, or intermittent, as shivering. A

minor source of heat is an increased activity of the glands of the body, and there is also evidence that prolonged cooling results in increased activity of the thyroid gland, which liberates a large quantity of thyroxine with resulting increased metabolism and heat production

Reaction to heat consists almost wholly of increase in heat dissipation, which is brought about by dilatation of the cutaneous vessels, and an increase in sweat secretion causing heat loss by evaporation. There appears to be very little provision for decreasing heat production, in fact an increase in temperature tends to accelerate metabolism and so unless this can be in some way compensated, to a further increase

RISE IN TEMPERATURE

A rise of body temperature above the normal limits can be caused in various ways. From what has just been said it is clear that if external warmth is applied and heat loss is prevented the temperature must go up. This occurs in heat-stroke, when a high external temperature combined with heat loss which is inadequate on account of a moist atmosphere or excessive clothing may cause such pyrexia as to produce coma and death. It is also possible to raise the body temperature by the passage through the body of high frequency electric currents. These encounter high impedance in passing through cell membranes and so liberate large amounts of heat, more than the cooling mechanisms are able to dissipate.

Besides these physical methods of raising the temperature there are certain chemical substances which cause a rise of temperature when they are present in the circulation. Among such substances are included many proteins and their breakdown products and particularly, bacterial toxins. It is a familiar fact that the presence in the body of disintegrating blood clot or necrotic muscle (as after cardiac infarction) causes a raised temperature in the absence of infecting organisms, and the height of the temperature may give some indication of the extent of necrosis. But by far the most common cause of a raised temperature is the presence in the body of bacteria, with the resulting liberation of toxins or other bacterial products.

into the circulation. These substances do not impair the functional capacity of the heat regulating mechanism. They only cause it to maintain the body temperature at a higher level, and the initial rise is produced by a decrease in heat loss. This decrease is effected by vasoconstriction in the skin. This in turn renders the skin cold and so stimulates the sensory end organs there and sets up reflex shivering so increasing the temperature further. Finally, the blood reaches the raised temperature which the thermostatic mechanism is now to maintain, and any tendency to rise further is stopped by the normal heat dissipatiooo processes so that the patient becomes flushed and feels warm.

The increase in body temperature causes an increased basal metabolic rate and an increase in urinary nitrogen. This increase is in purines and creatine as well as in urea, it is provided by the breakdown of tissue protein and is accompanied by loss of body-weight. Respiratory rate and pulse rate are increased and the blood pressure falls, partly from dilatation of the peripheral vessels and partly from reduced efficiency of the heart.

Whether the raised body temperature which accompanies so many bacterial infections is beneficial or harmful to the subject is a question which is much in dispute. There seems no doubt that a raised temperature increases the ability to destroy certain micro-organisms. It increases the phagocytic capacity of the reticulo endothelial system, it increases the rate at which immune bodies are formed and it lessens the viability of micro organisms. The last is commonly made use of in the pyrexial treatment of neurosyphilis. On the other hand an excessive temperature causes great discomfort, and in certain disorders, such as enteric fever, cooling by cold baths or sponging may actually aid recovery as well as increase the patient's comfort.

An effect of pyrexia which is not always realized is the wastage of tissues which it entails. When the blood temperature is raised its oxyhaemoglobin is dissociated more easily at the oxygen tension which is found in the tissues. This leads to increased oxidation of the tissues and a need for larger

amounts of foodstuffs which in conditions of disease are difficult to assimilate. A lower temperature will be accompanied by less tissue oxidation and thus by less need for an increased diet.

All these considerations tend to show that some control of pyrexia is of value in combating disease, although moderately high temperatures are harmless and may be even beneficial. Exact limits are difficult to lay down and probably vary in different diseases, but a working rule might well be to maintain the body temperature between about 101° and 103° F. This obviates the harmful effects and discomfort of extreme hyperpyrexia without losing the advantages of a moderate degree of fever. Control can be exercised by external cooling or by the use of antipyretic drugs.

METHODS OF CONTROL

External cooling has been used in many febrile conditions but is said to be of particular benefit in enteric fever. The patient is immersed in a tepid bath and at the same time the skin is rubbed briskly. The effect of this friction is to prevent the cutaneous vasoconstriction which would otherwise occur and would prevent the blood from being effectively cooled by the bath. Cooling can be continued until the patient feels cold but should be stopped if shivering occurs. Less drastic cooling can be carried out by a cold pack or by sponging with tepid water. In each case the object is to apply external cold without causing the vasoconstriction which would prevent the cold water from cooling the blood stream.

In *heat-stroke* the temperature regulating mechanism has broken down completely. The higher the temperature rises the greater the metabolic breakdown and more heat is set free. The only means of dealing with this condition is the application of external cold and this is best done by rubbing with ice, or by blowing air by a fan on to the wet body. In either case it is important to remember that as the temperature falls less heat will be formed by metabolism. Cooling goes on with an acceleration and the application of cold should cease

when the temperature has fallen to about 103° F. or it may fall much too low and cause collapse

When, however, pyrexia is due to disease, that is to say to the presence of abnormal substances in the blood stream, the temperature regulating mechanism is still functioning. It is in fact to the effect of these substances on the nervous mechanism that the pyrexia is due, and it is in such conditions that the *antipyretic drugs* cause the temperature to fall. From what has been said it is clear that the quantity of heat produced in the body is very difficult to control. Diminution of heat production is a slow process, ill adapted for the varying conditions of life, and only brought into action by lasting changes of environment.

ACTION OF DRUGS

Adaptation to the needs of the moment is carried out by changes in heat dissipation by nervous control of the circulation through the skin and of the sweat glands. The antipyretic drugs act on the nervous mechanism of heat stabilization and they lower febrile temperature by causing an increase in heat loss. It was at one time believed, from the experiments of Gottlieb that quinine was an exception to this rule, and that it caused a decrease in heat formation but this view is no longer generally held. Except as regards its special action on the malarial parasite the antipyretic effect of quinine is produced in essentially the same way as that of the other drugs which are used for this purpose, although there is some evidence that quinine acts on a lower part of the vasomotor mechanism than do the other drugs, since it causes some lowering of a febrile temperature after high section of the spinal cord. Other antipyretics fail to effect this and it is universally agreed that the fall of temperature which follows their administration is due to an effect on the cerebral part of the heat-regulating mechanism situated in the hypothalamus, resulting in an increased heat loss through dilatation of the cutaneous vessels. This dilatation is confined to the vessels of the skin and does not lead to a fall of blood pressure, which is of course mainly dependent on the calibre of the visceral vessels.

DRUGS AVAILABLE

It is convenient to divide the antipyretic drugs into three groups differing in their structure and to some extent in their effects. These groups are —(1) The salicylates, (2) the amido-pyrine group, (3) the acetanilide group.

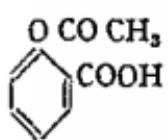
THE SALICYLATES — From early times preparations of the bark of the willow (*Salix*) were used in the treatment of fevers and rheumatism and in 1830 an active glucoside, salicin, was extracted from it. *Salicylic acid* was prepared from salicin in 1838 and was synthesized in 1860, and for many years there was acute controversy as to the relative merits of the "natural" and synthetic acids. It is now universally agreed that their

effects are identical. It is chemically ortho-hydroxybenzoic acid, and has the structural formula shown here, and it is a rather curious fact that the isomeric meta and para compounds are devoid of physiological activity. The acid is itself too irritant for internal use and is always given as a salt, usually of sodium and prescribed with added bicarbonate to ensure that no free acid is liberated in the stomach. Sodium salicylate acts as an antipyretic in all febrile states, but its effect is much more marked in acute rheumatism than in any other disease.

In other fevers other antipyretics are usually preferred, owing to the undesirable results which sodium salicylate often brings about. These results are unavoidable and always result from adequate dosage. For an adult 20 grains may be given every two hours with at least an equal quantity of bicarbonate, until toxic symptoms develop. These at first consist of nausea and tinnitus. The nausea may go on to vomiting and there may also be headache and vertigo. Some albuminuria is usual, and there is a decrease of urinary excretion with water retention in the tissues. Large doses may cause nephritis. The onset of these symptoms, especially of vomiting, may make it necessary to cease or reduce the administration of the drugs but, unless it is quickly resumed the temperature will rise again, and it is highly desirable to keep up the concentration of salicylate in the blood for some time after rheumatic symptoms

have disappeared. Regarded only as antipyretics, some of the derivatives of salicylic acid are of more importance than the acid itself. The most familiar is acetylsalicylic acid, which is marketed under various trade names of which the most familiar is "aspirin."

Acetylsalicylic acid has the structural formula shown here,



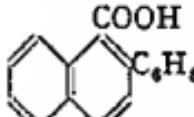
and it has a more powerful antipyretic and analgesic action than the salicylates. Its insolubility and rather greater toxicity make it unsuitable for use in the large dose necessary in acute rheumatism.

There is some uncertainty as to its exact fate in the body, and it probably differs in detail in different individuals and conditions of the alimentary canal when it is taken. It is capable of being hydrolysed in normal stomach contents, and a part is probably so broken down with the liberation of free salicylic acid and consequent gastric irritation. Some samples even contain free salicylic acid, and this probably explains the differences which many persons find in the liability of acetylsalicylic acid to cause indigestion, and it has recently been asserted that examination by the gastroscope shows inflamed patches of gastric mucosa where particles of acetylsalicylic acid are resting on the surface. It is certain, however, that a part of what is ingested is absorbed from the alimentary canal unchanged, and after large doses it is said that 25 per cent of the salicylates of the urine consists of unchanged acetylsalicylic acid. The differences between the analgesic and toxic effects of acetylsalicylic and salicylic acids bear out the same conclusion.

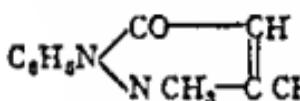
As with the other antipyretic drugs, these analgesic effects are regarded to-day as of much more importance than the antipyretic effects for which they were at first introduced. In the case of acetylsalicylic acid this effect is a matter of common knowledge, and severe pain may be controlled by adequate dosage. The irritant action on the stomach can be avoided to some extent by the use of the soluble calcium salt. Other toxic effects are not common, and consist chiefly of various skin conditions, especially oedema of the face and respiratory mucous membrane, with possibly urticaria. These conditions are pro-

duced by small doses in susceptible persons, but the idiosyncrasy is rare

A substance which is allied to the salicylates and is about equally effective as an antipyretic is *cinchophen* or phenyl-

 *quinoline-carboxylic acid*, as shown. Its main action is to lower the renal threshold for uric acid excretion and so increase the uric acid excretion. It was introduced as a remedy for gout but it has to be used with great care on account of its liability to cause a toxic hepatitis with yellow atrophy

THE AMIDOPYRINE GROUP—This group includes the first substance which was synthesized for use as an antipyretic drug. It was named by the maker "*antipyrin*" and has been placed in the Pharmacopoeia under the name of *phenazone*. It

 is a derivative of pyrazolone and has the formula shown here. The only other member of the group which is much used in this country is *amidopyrine*, in which the H of the pyrazolone ring is replaced by N(CH₃)₂. Both substances cause an increase in heat loss in fever through dilatation of the cutaneous vessels, as has been already described for the salicylates. Both are markedly analgesic and are used for this purpose more than for their antipyretic effect. *Phenazone* acts on a part of the temperature regulating mechanism which is situated in the brain. Unlike quinine it has no antipyretic effect after high section of the spinal cord. It is particularly liable to cause skin rashes, and some individuals are unable to tolerate quite small doses on this account. The rash usually takes the form of rounded erythematous patches, which may become bullous. On recovery a pigmented area is left, but such an area quickly becomes erythematous again if another dose is taken. Large doses may cause collapse.

Amidopyrine is sometimes known by its trade name of *pyramidon*. It has antipyretic and analgesic properties very like those of phenazone and is slightly more effective. It has not so great a tendency to cause skin rashes, but it is now

known to be prone to cause in susceptible persons the very grave condition of agranulocytosis. This consists in a marked decrease in the number of polymorphonuclear leucocytes, which may disappear completely from the circulation. The symptoms of the disease are severe inflammation and ulceration of the pharynx and throat, with fever and collapse. The reasons for the special idiosyncrasy of certain individuals are not known. It has been stated that women at or after the menopause are especially liable, but the number of cases is fortunately too small for statistical certainty. Prognosis depends chiefly on the degree to which the condition has advanced before it is detected, and patients who are taking amidopyrine regularly should undergo a blood examination at intervals since there is usually a marked drop in the leucocyte count before other signs appear. This dangerous possibility is now generally recognized and amidopyrine is used with caution but it is not so widely known that amidopyrine is a constituent of a number of analgesic drugs which are marketed under trade names and which entail the same dangers. The presence of the other drug, usually a soporific, with the amidopyrine reduces the dosage of the latter and thus its danger, but exceedingly small doses are enough to cause dangerous reactions in susceptible subjects.

These compounds or mixtures include — *Veramon*, in which it is compounded with barbitone, *cibalgin* in which it is compounded with diethylbarbituric acid (or 'dial'), *dismenol* or amidopyrine and parasulphamidobenzoic acid and *allonal*, amidopyrine and allyl isopropylbarbituric acid. The quantity present in each of these is harmless to normal subjects but may be dangerous if given to persons who have an increased susceptibility as the result of a previous attack.

A closely allied compound which is claimed to be free from the risk of causing agranulocytosis is "isopropyl antipyrin"

which has the formula shown here

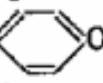
$$\text{C}_6\text{H}_5\text{N} \begin{cases} \text{CO} & \text{C CH(CH}_3\text{)}\text{,} \\ & \parallel \\ \text{N CH}_3 & \text{C CH}_3 \end{cases}$$
 It will be seen that it is closely related to amidopyrine but does not contain the $\text{N}(\text{CH}_3)_2$ which is believed by some authorities to be responsible for agranulo-

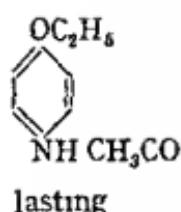
cytosis It is marketed by the makers as a constituent of a analgesic which they call *saridone*

THE ACETANILIDE GROUP—These drugs are sometimes known as the coal tar antipyretics, from their chief source They cause a lowering of febrile temperature by the same mechanism as the members of the preceding group The substitution of a hydrogen in the benzene ring by an OH or an NH₂ confers on the substance a strong antipyretic and analgesic activity, but the simple compounds, such as aniline or phenol, are too drastic for therapeutic use and cause collapse Their action is modified by replacing one of the H atoms in either or both of these side chains by some other radical, and in practice it is found best to choose either C₂H₅ or CH₃CO for this purpose

A number of such compounds have been synthesized One of the earliest was *acetanilide*, as illustrated It has powerful

 antipyretic and analgesic properties but has been found dangerous as compared with other members of the group It was put on the market under the name of *antifebrin* and is used as an ingredient of many proprietary 'headache powders' A number of cases of acute and chronic poisoning have been reported and it has also occasionally caused an addiction, with serious excitement symptoms on discontinuance Acute poisoning causes symptoms of collapse with circulatory failure, chronic poisoning causes mental and physical weakness, leucocytosis, and in particular a cyanosis which is generally believed to be due mainly to the formation of methaemoglobin although the presence of sulphhaemoglobin has been described in some cases Cyanosis may begin within a few days after the drug is first taken and increases gradually with continued administration It may take a fortnight to disappear

All the members of this group are believed to produce their therapeutic effects through being converted in the body  to paramidophenol as indicated and all of them are derivatives of this substance The best known and most typical is perhaps *phenacetin*, shown here



In this drug the drastic action of the paramido-phenol has been modified by the replacement of a hydrogen in each side group, so that the production of paramidophenol in the body is delayed and prolonged, and its effects are less drastic and more lasting

A large number of similar derivatives of paramidophenol are now available, and it is superfluous to enumerate them. Their effects differ in degree only, and can be guessed in each case from their constitution on certain general principles. These may be summarized as follows

- (1) Toxicity and therapeutic efficiency run more or less parallel.
- (2) Toxicity is more reduced by the substitution of an alkyl group (e.g. C_2H_5) than by substitution of an acidic group (e.g. COCH_3).
- (3) Toxicity is more reduced by a substitution in the NH_2 group than in the OH group.
- (4) Reduction of toxicity is proportional to the size of the group introduced.

The toxic effects have already been described. They consist of methaemoglobinæmia and cyanosis in a few cases and occasionally collapse when overdoses have been given. Signs of circulatory failure may be due to a cessation of the stimulant effects of high temperature as a result of the antipyretic action, and it is not advisable to lower the temperature very far or very quickly.

HOW TO REDUCE TEMPERATURE

For the purpose of bringing down a febrile temperature 5 to 10 grains of either phenacetin or phenazone may be given every two hours until the temperature reaches the level desired. For the reasons given on page 182 of this article, that level should not be below about 103°F . When that level is reached smaller doses may be used at less frequent intervals. Each dose produces its maximum effect in about two hours and wears off in about eight hours.

All these substances are, however, much more widely used as analgesics, mixtures of phenacetin and acetylsalicylic acid with a small amount of either codeine, caffeine, or quinine being well known. It is believed by some that such mixtures are less

toxic and more analgesic than would correspond with the sum of their components, but exact valuation is difficult

UNDESIRABLE EFFECTS

Apart from the more serious toxic effects some undesirable results of these drugs are fairly common. They include profuse sweating and chills resulting from the methods of heat loss and the results of irritation of the stomach and kidney. Erythematous rashes and stomatitis are also met with, particularly after phenazone and the liability to them increases with repeated use.

The analgesic effect of both the amidopyrine and acetanilide groups of drugs is marked and is much more valuable than their effect on pyrexia. It is most noticeable in pains of a rheumatic or neuralgic origin and particularly in headache. They are much less effective in pains due to injury. The mechanism of their action is obscure. They do not generally cause drowsiness and do not reinforce the action of the ordinary hypnotics. On the other hand they are found by psychological tests to cause impairment in mental efficiency. They prolong reaction time and decrease cutaneous sensibility. There is some evidence that they affect the calibre of the meningeal vessels and if this is so it might explain their marked action in the relief of headaches since these are now known to be due in many instances to disturbances of the cerebral circulation.

THE SULPHONAMIDES

The relation of the *sulphonamide group* to the antipyretics is still a subject of discussion. It is common knowledge that the sulphonamides are bacteriostatic rather than bactericidal and it is believed by many that in the body their function is to check the proliferation of bacteria rather than to destroy them. The latter is carried out by the usual defence mechanisms. If this is so the rapid fall of temperature which sulphonamide therapy so often effects must be due to an antipyretic effect of the drugs rather than to destruction of the infecting organisms. Several writers have claimed that the output of antibodies occurs at the same period of the disease whether sulphonamides

have been used or not, and that the amount of their output is not affected by the treatment. Clinical experience moreover shows that sulphonamide treatment must be persisted in for some time after the temperature has fallen to normal.

OTHER ANTIPYRETICS

In addition to the specifically antipyretic drugs which have been dealt with so far, several others have an effect on febrile temperatures which is secondary to other processes. The action of *Dover's powder* is familiar and its effect in fever is probably due to the cutaneous vasodilatation which increases heat loss. Its action is due to its opium content. A similar effect is produced in fever by the nitrates or organic nitrates. In health the heat loss caused by the cutaneous vasodilatation which they cause is at once compensated by increased production, but in fever the mechanism seems to be less readily responsive and some fall in temperature usually occurs. Such drugs have very little action on the temperature-regulating mechanism and their effects are more comparable with those of cold applications to the skin.

CONCLUSIONS

It will be clear from what has been said that all the antipyretic drugs and methods are concerned more with decreasing the patient's discomfort than with actual therapy. It is only in exceptional cases that the body temperature becomes so high as to be in itself a source of danger. When such hyperpyrexia is caused by the action of organisms on the thermostatic mechanism it can be usefully controlled by drugs, and if the temperature can be kept down to about 103° F the patient will probably be benefited. The chief use of such drugs, however, is without doubt in the control of pain, and it is in this direction that advances may be hoped for.

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CHAPTER XV

COUNTER-IRRITATION AND COUNTER-IRRITANTS

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CHAPTER XV

COUNTER-IRRITATION AND COUNTER-IRRITANTS

FOR centuries stimulation of the skin by mechanical or chemical means has been used in the treatment of disease. To-day the hot-water bottle and electric blanket have largely replaced the hot brick, and infra red radiation the seton, but the relief they produce is similar, although views on the mechanism by which relief is brought about have undergone many changes. There is probably no fundamental difference between the counter-irritant effects produced by mechanical and physical methods. Lewis (1927) has shown that when the skin is irritated by any means a substance closely allied to histamine is liberated, and it is this that gives rise to the phenomena observed, such as local reddening, oedema, and rise of skin temperature. A similar, although probably not identical, mechanism is responsible for the later effects, such as blistering. This essential similarity in the effects produced by all methods of counter-irritation allows the choice of the actual method to depend upon such considerations as accessibility, convenience, and the psychological reactions of the patient.

It is claimed that counter-irritation produces two main effects. In the first place pain is relieved, and in the second the underlying disease process is beneficially affected. It is easy to confirm the former claim, for it is within the everyday experience of the practitioner. The latter is much more difficult to substantiate, as will be seen on page 196.

THE MECHANISM OF COUNTER-IRRITATION

The explanation of the action of counter-irritation is closely connected with the concept of "referred pain". It is a well-known fact that pain arising from a lesion of the hip joint may be "referred" to the knee or from a carious tooth to the skin.

of the face. This concept was extended to visceral pain by Mackenzie and by Head. Mackenzie believed that the viscera were themselves insensitive to painful stimuli but, when they were attacked by disease, impulses ascended to the cord producing an "irritable focus" from which the pain was referred to the skin having the same segmental innervation as the viscous. On this view counter-irritation acts by putting into the "irritable focus" in the cord new impulses from the skin of a more easily bearable type, which tend to occupy the common path to the analysing centres in the thalamus and cerebrum, and so to exclude the pain arising from the viscous. In addition, impulses may pass from the irritated skin to the cord, and thence to the diseased viscous, affecting it beneficially. Recent work, however, by Morley (1931), and Lewis and Kellgren (1939) has thrown doubt on the validity of the generally accepted views of the mechanism of visceral pain. Indeed, the latter observers conclude that there is no special form of pain, referred or otherwise, which is the hall mark of visceral disease, and that pain of visceral and somatic origin cannot be distinguished as such. These observations do not negative the current views as to the mechanism of the relief of pain by counter-irritants, but they throw doubts upon the necessity of applying them to a well defined area appropriate for each given viscous. Diagrams of such areas are given in many textbooks. Recently it has been shown by Hardy, Wolff and Goodell (1940), who have devised a simple method for the measurement of pain, that the threshold for pain can be raised by 35 per cent if a second painful stimulus is simultaneously introduced, even if it arises from a distant focus. This suggests that the action of counter-irritants depends fundamentally on the limited ability of the analysing centres to experience simultaneously two sets of painful stimuli, whether they enter the cord at the same level or not. In actual practice, however, counter-irritants are found to give greatest relief when applied to the area at which pain is actually experienced.

It is when the claim of counter-irritants to affect deep-seated disease processes beneficially is considered that greater difficulties arise. A nervous pathway does exist whereby sensory

impulses arising in the skin may produce reflex alterations in the blood supply of deep-seated organs. The evidence that this actually occurs to any effective extent is, however, much less strong than is commonly supposed, and the simple hyperæmia which can be produced would not necessarily have a beneficial effect on disease processes. The observation of Burton Opitz and Lucas (1909), for example, that heating of the skin of the loin causes reflex hyperæmia of the kidney, is often quoted in support of this view. These observers, however, also showed that cooling of the skin has the reverse effect, yet the application of ice packs to the loin is alleged to be as effective a form of counter-irritation as the application of heat. There is, in fact, no satisfactory evidence that visceral lesions heal more rapidly if counter-irritants are applied to the skin overlying them. The explanation of this time-honoured view is probably due to a natural tendency to interpret the relief of pain as an indication that the condition giving rise to the pain is undergoing improvement.

In addition to the treatment of visceral disease, counter-irritation is used in the treatment of more superficial lesions, such as boils and bruises, and here the clinician is on surer ground. Not only is pain relieved by the mechanism already described, but there is much evidence that heat, for example aids the resolution of inflammatory processes. Counter-irritation may give rise to more wide-spread effects, exciting, for example, the medullary reflexes, as when respiration is stimulated by a cold douche. These general effects are the basis of the use of stimulation of the skin, as by heat in shock and collapse.

INDICATIONS AND CONTRAINDICATIONS FOR COUNTER-IRRITATION

From what has already been said it will be realized that the main indication is pain or discomfort. The method is of clear value in treating superficial lesions, such as *boils* and *bruises*, and in painful lesions of the muscles, nerves, connective tissues, tendons and joints, such as *tenosynovitis*, *fibrositis*, *neuritis* and various forms of *arthritis*. Relief is usually afforded in *visceral*

pain, such as intestinal and renal colic, *menstrual pain*, and pain arising from *inflammation* of the *lung and pleura*. In the majority of cases, however, the method should be supplemented by the administration of analgesic drugs, either the anodyne antipyretics, such as *aspirin* or, in more severe cases, one of the opium alkaloids.

Contraindications—Counter-irritation, and in particular the application of irritant drugs, should be used with caution in patients with sensitive skins, more especially in children and in those liable to peripheral vascular disease, for example, diabetic patients and the older age groups.

METHODS AVAILABLE

The methods available for counter-irritation may be divided into physical and chemical. Among the former are included the application of heat and cold, cupping and the use of radiant heat, infra-red radiation, diathermy and ultra violet light. The chemical substances available for application comprise a large number of drugs which have the common effect of producing cutaneous irritation in greater or lesser degree. The actual method of counter-irritation chosen will depend largely on the type of lesion which is to be treated and on the availability of the appropriate apparatus. It must not be forgotten, however, that the psychological element is often great and may well explain individual enthusiasm for one particular form of treatment.

PHYSICAL METHODS

HEAT—The application of heat in one form or another is the most common form of counter-irritation, and it is certainly one of the most effective. The heat may be applied either moist as, for example, by fomentation, poultice or cataplasma kaolini B.P., or dry heat may be used for example the electric blanket, radiant heat, infra-red radiation, or diathermy.

The fomentation, although time honoured has many drawbacks. It retains its heat for a short space of time and, if applied to open septic areas, tends to diffuse the organisms. For this reason boils should never be fomented.

The linseed poultice retains its heat for a longer time but has substantially the same defects. It is made by mixing about three-quarters of a pound of linseed with one pint of boiling water and applying about half an inch thick on lint.

Cataplasma kaolin: B.P. (antiphlogistin) should be applied thickly. It retains heat relatively well and contains counter-irritant substances and antiseptics which increase its effect and safety.

The above three methods probably act partly by their splinting effect, as they immobilize the affected part, and the beneficial results they undoubtedly produce on occasion is often due to this, rather than to their somewhat limited capacity to convey heat.

Simple immersion in hot water of the affected part may occasionally be an effective method of applying heat. Thus a septic wound may be immersed in a bath containing water as hot as can comfortably be borne. An antiseptic, such as hydrogen peroxide, should be added and additional hot water poured in from time to time to maintain the temperature.

The electric blanket is a suitable method of applying heat to relatively large areas of skin for the relief of deep pain of the "rheumatic" type. Its temperature should be thermostatically controlled.

Radiant heat can be applied simply in the home from an ordinary electric fire or electric light bulb, but care must be taken to avoid burning. Special apparatus is required if it is desired to use only the infra-red (non-luminous) rays. There is, however, some dispute as to whether the longer or shorter heat waves produce the more desirable therapeutic effects.

Infra red radiation gives rise to a painless and pleasant sensation of heat. Beaumont (1936) concluded that for the relief of pain it far surpasses any other form of treatment. The reader is referred to his book for details of indications and methods of use.

All the above measures act essentially by stimulation or mild irritation of the skin and the heat is rapidly removed by the blood in the superficial vessels. If it is desired to affect the deeper tissues *diathermy* or *ultra short wave therapy* must be

used. These methods are of undoubted value but are not strictly forms of counter-irritation, and the reader is referred to specialized articles for details.

COLD—This may be applied as an evaporating lotion, a cold compress, or as an ice pack. Greater relief is sometimes afforded than by heat, and this method is well worth a trial in, for example, bruising or painful pleurisy.

OTHER PHYSICAL METHODS

Ultra violet radiation may be applied locally for its counter-irritant effects to relieve such conditions as boils or fibrositis. An overdose easily produces blistering and, unless given by a fully experienced practitioner, this method has a smaller margin of safety than those already mentioned.

Dry cupping is still occasionally used for small lesions, such as boils, and for the relief of localized, deep-seated pain. It possesses no obvious advantages over more simple methods.

Leeches produce a profound psychological effect and occasionally, as when applied over the painful liver of congestive cardiac failure, give surprising relief.

CHEMICAL SUBSTANCES USED AS COUNTER-IRRITANTS

A large number of substances have been, and still are, used as counter irritants. They have the common property of irritating the skin and, most probably, they all act by causing the release of a substance closely allied to histamine. They are commonly classified as *rubefacients*, *vesicants* and *pustulants*, according to the severity of the effects they produce. The last class are not now used and the vesicants are little used by the present day practitioner. Almost all irritants may give rise to blistering if applied in a too concentrated form or for too long a time. Except with cantharides, the blisters heal slowly and care is usually taken to avoid this effect. Many of the milder rubefacients are applied in combination especially in the form of liniments. *Liniments* are usually well rubbed into the skin and the massaging effect so produced is an undoubted adjuvant to their therapeutic action. Sometimes counter-irritants are

first applied, and the part is then covered with strapping or cotton-wool. It has been shown by Taylor (1923) that the rubefacients do not raise the subcutaneous temperature, and their action is therefore entirely superficial. The subcutaneous temperature can, however, be raised by covering the skin with cotton-wool and, in treating relatively superficial lesions, the application of such a dressing may aid the effect of the counter-irritant. The following are the more important substances which are used as counter-irritants —

TURPENTINE is the most commonly used representative of the volatile oil group. It has the merit of cheapness combined with efficiency. Blisters occur after prolonged application only, but must be avoided, as they heal slowly on account of the power of penetration of turpentine. Its mild antiseptic action is at times of value. It can be effectively applied as a "stuve," that is, on flannel wrung out of hot water containing turpentine. Especial care must be taken to avoid too prolonged application.

CAMPHOR has a pleasant smell and is widely used in liniments for the treatment of bruises, sprains or fibrosis. It rarely produces blistering.

MUSTARD contains a non-irritant glycoside which, in the presence of water, is acted on by an enzyme also present in mustard to produce volatile oil of mustard (allyl isothiocyanate). The oil is intensely irritant and penetrates, readily producing blisters which heal slowly. Mustard is best applied as the plaster, which is immersed in warm water a few minutes before application and applied for from fifteen to thirty minutes. Mustard may be added to a linseed poultice to enhance its effect.

CANTHARIDES can be applied as the plaster or as liquor epispasticus. The plaster must be applied for about eight hours for blistering to occur and is best removed at about six hours. The liquor should be applied for short periods only, and with special care. The blisters are relatively painless and, due to the poor power of penetration of cantharides, they heal rapidly. Vesication is much less valued as a form of treatment.

nowadays than formerly, and indeed it is difficult to justify on any modern view of counter-irritation

IODINE may be applied as the strong tincture (liq. iodi fortis) for its counter-irritant effects. Iodine is said to be rather milder in its action than most counter-irritants but, if the patient has a sensitive skin or if part is covered so that evaporation of the iodine is prevented, it may give rise to serious and painful blistering. When the skin is broken neither the strong nor the weak tincture should be used.

METHYL SALICYLATE (oil of wintergreen) is a common constituent of liniments for the relief of muscular or articular rheumatism. A little is absorbed through the skin but certainly not enough to have any general action. The smell of this substance is closely associated in the public mind with "rheumatism," but it is doubtful if it has any advantage over other counter irritants in this form of disease. Dilute methyl salicylate ointment (Ung. methyl sal. dil., B.P.C.) may be combined with an equal part of non-staining iodine ointment (Ung. iodi denigrescens, B.P.C.) to give a mild counter-irritant and antiseptic effect. The dark colour renders the preparation attractive to some patients.

MERCURY is often applied as Scott's dressing (Ung. hydrarg. co.) which contains metallic mercury and camphor. It is used mainly for sprains and bruises. Some mercury is absorbed which might presumably be of value if the patient had coexistent syphilis.

CHLOROFORM is a powerful vesicant if evaporation is prevented, but when evaporation is free it has a mild rubefacient action only.

ALKALIS, and in particular *ammonia*, are occasionally used as counter irritants as constituents of liniments.

LINIMENTS contain one or more of the above substances in combination, in either an oily or aqueous vehicle. Some contain, in addition to counter-irritants, substances such as aconite, belladonna or opium, in an attempt to produce a local anodyne action. Such an effect would be of value in treating lesions such as bruises and sprains, but the evidence of its

existence is scanty. Too little attention has been paid to the careful observations on human subjects by Short and Salisbury (1910), who failed to demonstrate any such action. If, as seems highly probable, all the counter-irritants act by the release of a common histamine like substance in the skin, the choice of a liniment should be determined by the intensity of action it is desired to produce, and by cheapness. The following is a selection of liniments with their active constituents indicated (where not obvious from the name) in order of ascending price.

Lin saponis B P (camphor), Lin album B P C (turpentine), Lin terebinthinae B P (camphor and turpentine), Lin camph B P, Lin ammoniae B P C (ammonia), Lin aconiti oleosum B P C (aconite, belladonna and chloroform), Lin meth sal B P C (methyl salicylate, menthol, camphor, eucalyptus), Lin chloroformi B P C (chloroform and camphor). There seems no reason to believe that a greater use of the cheaper members of the series would lead to a diminished rate of recovery in the conditions for which they are applied.

An advisory committee set up by the Government has recently decided (1940) that the following substances which have been dealt with here, are non essential and do not justify their importation or manufacture in war time. The suggested substitute is given in brackets. Cantharides and cantharidin (mustard), linseed poultice (*Cataplasma kaolini*), oil of pine and oil of camphor (turpentine), aconite (benzocaine).

CONCLUSION

To sum up, counter-irritation is a potent method for the relief of pain. There is little evidence that it beneficially affects lesions of deep seated organs but considerably more that it is of value when the damage is superficial, as in furunculosis or bruising. The choice of method of application depends on availability and personal predilection. Heat in one form or another is almost always acceptable. The counter-irritant drugs differ in intensity of action but produce essentially the same effects. In making a choice it is reasonable to take into account their relative cost and, at the present time, the ease with which they can be manufactured or imported.

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CHAPTER XVI

SOME MODERN DISINFECTANTS AND ANTISEPTICS

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CHAPTER XVI

SOME MODERN DISINFECTANTS AND ANTISEPTICS

THE substances dealt with here are potent in killing bacteria or preventing their growth outside the body and so are truly bactericidal or bacteriostatic, they act locally (The sulphonamide group would probably never have been selected for therapeutic trials on account of antiseptic properties) A laboratory worker may appear unsuited to deal with this subject, but its study has been much neglected by others Surgeons of the present day can claim to be Lister's grandchildren and great-grandchildren, and filial piety is so strong in some that to throw doubt on carbolic acid (phenol) as the antiseptic of choice seems almost like sacrilege Many apply to wounds various drugs such as boracic acid, iodine, eusol, various phenol analogues or mercury compounds, but it is generally not clear whether or not these are regarded as equivalents differing merely in the appropriate concentrations The chief reason for this position appears to be that until fairly recently no genuine therapeutic effect was to be expected from the available disinfectants and antiseptics, and they were assessed almost solely by their capacity to kill *in vitro* suspensions of bacteria in water Organisms were exposed to a standard solution of phenol and, in parallel, to varying dilutions of the antiseptic under test, the greater the dilution which killed organisms in the same time as was taken by the phenol solution, the higher the efficacy of the new antiseptic was reckoned Then it was realized that if substances were to act as therapeutic agents, account should be taken of the fact that they must influence bacteria situated on the surface of various tissues or in their depths These conditions impose severe demands upon the antiseptic Although a compound were highly bactericidal *in vitro* it might fail *in vivo* because it was too poisonous for the

host either from damage to tissues locally or from toxic effects on vital organs when absorbed and distributed through the body. Also it might not be possible to bring it into effective contact with the infected site. So attempts were made to test antiseptics under conditions similar to those existing in life the organisms instead of being suspended in water or saline were suspended in serum a fluid rich in protein and similar to the lymph of the tissues. Many fairly powerful antiseptics suffer great reduction of their activity under these conditions mercuric chloride and other mercurials and iodine are striking examples.

But admixture with lymph is only one of the factors of account in infected tissues. The antiseptic might be fixed or decomposed by the tissues and thereby inactivated this will tend to happen especially when extensive tissue damage has occurred as the result of trauma or infection or an inflammatory reaction has led to accumulation of cells which may be degenerate or dead as in pus or living as in granulation tissue. Further any considerable mass of dead tissue such as the contents of an abscess or a portion of dead bone or other necrotic material cannot be thoroughly penetrated by an antiseptic by whatever route it is introduced. When the infection is in an inaccessible situation in an internal organ or a hollow viscus like the gall bladder the problem is to direct the drug to the infected site. Accordingly it must be clear that the need for surgical interference—incision, excision and drainage—cannot be obviated by the use of antiseptics. When infection is generalized in the blood stream there is so far no antiseptic which will control it except possibly in certain experimental infections in small animals e.g. mice infected with pneumococci and treated by optochin.

Obviously rational advances in the use of antiseptics depended on extensive study of their effects on living tissues and experimentally infected animals and as a result of work of this kind it appeared that therapeutic antiseptics were efficacious particularly in preventing the development of infection. Thus it has been proved that when pathogenic organisms, e.g. virulent streptococci or diphtheria bacilli are

introduced into recent wounds or streptococci into the peritoneal cavity it is possible to allow an interval after inoculation and then to intervene effectively, even by brief washing of the wound with the antiseptic or introducing a quantity of it into the peritoneum respectively. The animals appropriately treated survived indefinitely, whereas those untreated died from the infection within several days. In the case of the infected wounds treatment by washing similarly with isotonic or hypertonic saline had no effect on the course of the disease.

Such observations afford the clearest refutation of the view that antiseptics can only do harm when applied to infected tissues, and so are incapable of promoting the suppression of infection in wounds. However, the therapeutic antiseptics do not sterilize a wound in the sense in which contaminated linen in a basin can be disinfected. The best results are obtained generally by means of compounds which act as powerful bacteriostatic agents that is to say are capable in high dilutions of damaging selectively the vitality of the organisms and so enable the natural tissue defences to come into play. Thus the therapeutic effect is due to the cooperated action of the drug and the host. The efficacy in this respect of substances like phenol and mercuric chloride is much inferior to that of antiseptics such as acriflavine (better eusflavine*) and proflavine (Browning 1937). There is also a wide difference in their respective actions on the tissues, the former types are well known to be poisons both local and general whereas the latter are relatively harmless. There is much evidence for this, only several observations need be quoted.

The eggs of trout contaminated with the bacilli of fish furunculosis can be sterilized by a solution of acriflavine (1:2000) which does not impair the later development of the fish whereas the concentration of carbolic acid required to kill the bacilli (1:200) also destroys the life of the eggs (Blake 1930). Again it has been recorded by Francis (Albert *et al.* 1938) that human leucocytes remain actively motile in a 1:2000 solution of acriflavine or proflavine for periods up to 1½ hours whereas weaker solutions are bactericidal for streptococci under similar conditions.

* Eusflavine is the neutral salt corresponding to acriflavine and should be specified.

and within the same time limits (Garrod, 1938). In wounds under continuous treatment with euflavine or proflavine various types of cells were seen in division at distances from less than one thousandth to one hundredth of an inch below the actual growing surface (Blacklock, 1929).

Accordingly, antiseptics are now available which, as compared with the older types, are much more effective against bacteria, and at the same time less injurious to the tissues of the host, such are, among others, *euflavine* (*acriflavine*) and *proflavine*, *quinanil* (Armitage *et al.*, 1929) and *brilliant green**—all used in strengths up to 1:1000 in 0.85 per cent NaCl solution. It should be noted, however, that there is no universal therapeutic antiseptic. In selecting a suitable drug both the site of application and also, in certain cases, the nature of the infecting organisms must be considered. For instance, euflavine (*acriflavine*), proflavine, and brilliant green in a strength of 1:1000 can all be applied safely to the skin † or wounds of the subcutaneous tissues, on the other hand, only the first two should be introduced into the peritoneal cavity, where several ounces can be left without producing irritation, but here brilliant green is highly irritating. Euflavine and proflavine may also be applied to other more delicate epithelial surfaces, but preferably in higher dilutions, 1:4000–1:10,000, brilliant green should not be used for these. Again, Russell and Falconer (1940–41) have shown recently that 1:1000 proflavine in isotonic saline is practically harmless to living brain tissue, whereas euflavine or acriflavine in the same concentration causes necrosis and haemorrhage, just as do antiseptics of other chemical types.

PRACTICAL USES

In suggesting practical uses those compounds are mentioned of which there are extensive records by British workers. Although other drugs may be capable of yielding similar results, they will not be referred to because the experience of their use is more limited. Also, applications in medical treat-

* Specify as sulphate, zinc free.

† Acriflavine idiosyncrasy has been described (Young and Hawking, 1938), but appears to be rare.

ment and minor surgery will be stressed. First it must be emphasized that there are certain situations in which so far no known antiseptics have proved effective. Thus it is not possible to diminish the bacterial flora of the intestine by any antiseptic taken by the mouth or otherwise, apart from enemas acting locally. Again, the fossæ of the nose have a delicate mucous membrane which normally harbours few organisms, although when there is catarrh various bacteria tend to be numerous, attempts to influence the nasal flora by antiseptics are likely to irritate the mucosa and to predispose to infection rather than to diminish it. Also, no antiseptic administered by the mouth or by injection reaches the interior of the gall-bladder in effective concentrations.

Although a self-cleansing action of the skin has been described, in virtue of which bacteria placed on it soon cease to be recoverable, nevertheless pathogenic organisms, such as the pyogenic cocci, are not infrequently present on the surface and may also occur in the deeper layers of the epithelium. When an abscess discharges on to the skin, contamination of the surrounding area with pyogenic organisms readily occurs and in this way crops of satellite abscesses are liable to develop. To prevent this, cleansing with an antiseptic must be carried out with a minimum of delay, since organisms which have penetrated to the depths of the epithelium are probably never reached. Prolonged contact with watery solutions should be avoided because maceration favours bacterial growth. The advantage of an alcoholic solution, of course, is the rapidity of drying.

Iodine is undesirable because of its irritating effect, which in some susceptible individuals may lead to severe "burns," and at the best it is not a very effective antiseptic. The most powerful skin disinfectant is probably "*violet green*" solution, a mixture consisting of one half per cent each of crystal violet and brilliant green in 50 per cent spirit (i.e. tincture, B.P.C.), which should be painted on. It is devoid of irritating action on the skin, but it stains intensely both skin and fabrics. On bedclothes, however, it can be decolorized by a solution of bleaching powder. Bonney's (1918) method of preparing the

skin of an operation area consists in painting the part, usually six hours before, then applying a compress of lint soaked in the solution and covering with thin waterproof which is kept in position until the time of operation. This mixture may also be used with advantage as a "first-aid" application. Ferguson (1924-25) in South Africa found among mine workers prone to septic injuries that when, instead of alcoholic iodine, violet-green was painted as soon as possible on to wounds and the surrounding skin, and in the more severe injuries a protective sterile dressing applied, there occurred "a remarkable reduction in the number of shifts lost from accidents."

When actual *sepsis of the skin* exists, as in severely infected "seborrhoeic" eczema of the head or groin, Smith (1922) has recommended *euflavine* incorporated in starch poultices according to the following procedure —

4 tablespoonfuls of rice starch and 10 grains *euflavine* are mixed with a little cold water, 1 pint boiling water is added and the mixture boiled with constant stirring until it thickens. When nearly cold it is poured on to the dressing cloth so as to form a layer half an inch thick, when quite cold and set it is covered with a single layer of gauze or butter muslin and applied to the part. This is changed three or four times daily and at each change the part is bathed with 1:1000 *euflavine*.

The same treatment has been used with good effect in sycosis (unpublished). In staphylococcal infection complicating eczema of the toes and foot, whether superimposed on interdigital ringworm or not MacCormac (1940) applies a dressing of 1:20,000 *euflavine*.

To recent superficial wounds a suitable antiseptic should be applied as soon as possible. Whereas no doubt the majority eventually heal satisfactorily, nevertheless a number, apparently trivial at the outset are followed by serious infection out of all proportion to their extent. Further the discomfort, pain, and loss of working time caused by even mild infections are well worth avoiding. After removing foreign matter, a wet dressing should be applied consisting of gauze soaked with 1:1000 *euflavine* or *proflavine*. Care must be taken to apply the dressing soaking wet as described. It must not be forgotten that these antiseptics, as well as certain others, have an intense

affinity for cotton, as is shown by the latter taking on a deep colour when the solution is tinted. If, say from motives of economy, the gauze is moistened with only a minimal quantity of the solution and then wrung out, this becomes merely an application of dyed cotton and practically none of the anti-septic is free to act. The dressing must not be allowed to dry, accordingly, when the injury is of considerable area and there is no sepsis, a waterproof covering may be put on and redressing carried out at intervals of two or three days. *Slight burns* are treated similarly. Those who doubt the efficacy of these anti-septics should take the opportunity presented by a case of multiple superficial burns, similar in size and depth, to dress one lesion with euflavine as described above and another say with boracic lotion, and they will be able to compare the absence of pain and suppuration in the former with their presence in the latter (Graham, 1925).

In the case of *more severe injuries at a later stage*, if there is sepsis and so long as this is present, dressings should be changed once or twice daily, a waterproof covering not being required until the wound is clean and frequent redressing unnecessary (Bennett, 1922). For infected gunshot wounds, which had become highly septic in spite of other forms of treatment, Carslaw (1917-18) found the following procedure efficacious:

An "open" wound was secured with adequate drainage, any accessible foreign body being removed. Strips of gauze well soaked in 1:1000 euflavine (acriflavine) were lightly packed into the depths of the wound, which was then covered with folds of gauze similarly soaked the whole being covered with waterproof. The folds of gauze were changed once or twice a day, but the packing was as a rule not removed until forty-eight hours after introduction. Within from three to seven days all signs of inflammatory reaction in the surrounding tissues had disappeared and there was improvement in the patient's general condition, with extraordinary absence of pain. The discharge from the wound, which had diminished markedly in the first forty-eight hours, had almost entirely ceased and the sloughs had separated.

When such extensive wounds have to be dressed for a prolonged period, once a clean granulating surface has been obtained, the strength of the solution should be reduced as far as possible compatible with the maintenance of freedom from

sepsis, e.g. 1:5000 or weaker. The reason for this is that prolonged contact with a 1:1000 solution—probably aided by evaporation—may lead to the surface of the wound becoming covered with a yellow fibrinous pellicle and to delay of healing. The application of eusol dressings has been found to remedy this in two or three days by causing separation of the pellicle (Carslaw, 1917-18). Turner (1919) obtained similar success with euflavine in cases of septic comminuted fractures of the jaws.

For *burns*, when these are serious, local applications have come to be recognized as only part of the general treatment. Accordingly, reference is made here exclusively to the use of antiseptics in mixtures which are applied with a view to producing tanning effects as well as inhibiting the action of bacteria. When treatment in hospital is carried out immediately after burning, Wakeley recommends that when shock has been dealt with, the patient being anaesthetized with gas and oxygen in a warm operating theatre, the whole burned area should be thoroughly cleansed. By means of gauze soaked in warm normal saline, which is the only solution to be used, all blistered and dead epidermis is excised, special care being devoted to the margins. Then, the area having been dried with an electric drier, an aqueous solution containing a mixture of gentian (crystal) violet 2 per cent, brilliant green 1 per cent and euflavine 0.1 per cent is sprayed on and the surface is again dried, the spraying and drying are repeated. Usually the second application, followed by drying, suffices to produce a thin, supple tan. After eight or nine days, in cases which are not too extensive and severe, the tan loosens and gradually falls off in bits, leaving a healed area. (This method may avoid the harm from tannic acid when the hands or face are involved.) Complete dryness of the treated surface with exposure to the air throughout is essential. When there has been first-aid treatment with subsequent development of sepsis, the surface is cleansed and dealt with similarly. Wilson (1940a) recommends a single application of 10 per cent solution of silver nitrate preceded and followed by applications of 1 per cent crystal violet. For areas which cannot be constantly

exposed to air or easily kept dry, he finds the following jelly useful —tragacanth 2 parts, glycerin 10 parts, powdered charcoal (B D H activated) 15 parts, silver nitrate 0.5 parts, water to 100 parts. This is applied with or without a single layer of gauze mesh. For *burns of only moderate extent* Wilson (1940b) also used a jelly consisting of tannic acid 10 parts, glycerin 10 parts, tragacanth 3 parts, euslavine 0.1 part, and water to 100 parts, applied on dressings after appropriate cleansing of the burned area, as described above.

In the treatment of *tender raw surfaces*, especially of considerable extent, when dressing causes acute pain, a mixture consisting of 1 per cent proflavine oleate in liquid paraffin has proved valuable (Berkeley and Bonney, 1919). A thick layer applied on a single layer of gauze, or spread on the wound and the gauze then applied, adheres but does not stick and need not be changed for several days, when it can be painlessly removed. It can be used continuously.

For the *control of local sepsis in radium therapy* Charteris (1937) has recently found the mixture of proflavine oleate with liquid paraffin to be the best preparation. For application to cancer of the cervix a packing saturated with proflavine oleate keeps the radium in position. In ulcerated malignant conditions involving the skin, when local sepsis is present, it is used before implantation or superficial application of radium. Further uses are in preparing the skin for implantation of radium in a difficult situation, such as the inner canthus of the eye and for preventing the development of septic foci on the neck after treatment with a radium collar. An especially valuable application (Young and Charteris 1940) is in the treatment of malignant tumours of the accessory nasal sinuses. After exploration and operative measures directed to throwing the antrum, ethmoid cells and even the sphenoid sinus into one more or less regular cavity, a series of radium applicators are introduced and kept in position for seventy-two hours by packing. In consequence of the use of the proflavine-oleate paraffin mixture to soak the packing, all gross sepsis—with the attendant suffering and retarded convalescence—has been abolished when other procedures had failed. At the end of the time the packing

comes away without sticking and is reasonably clean and almost free from objectionable odour. As the authors state, it is not necessary to stress the importance of combating infection in a region subjected to radiation in dosage adequate to deal with malignancy. So remarkable a result, which has been consistently maintained, suggests other uses of this material in cases in which a temporarily closed cavity must be kept clean.

In *acute stomatitis* superadded as a rule on chronic septic mouth conditions, Turner obtained striking results by syringing out the mouth with a 1:1000 solution of eusflavine or proflavine, special attention being paid to all pockets. Then gauze soaked with the solution was lightly packed into the angle of the cheek and all around the gums and retained in the mouth for twenty or thirty minutes, the procedure being repeated thrice daily. Rapid relief of pain and subsidence of the acute inflammatory condition resulted. Further, in cases in which the mouth was so foul that the bad odour could be readily detected at a distance of several yards, twenty-four hours after beginning treatment the breath had become quite free from smell. Wells (1917) in an extensive investigation of preparations intended for checking the development of bacteria in the mouth, obtained the best effects with an aqueous mixture containing sodium desoxycholate 2 per cent, quinine 0.25 per cent and eusflavine 1:2000. Tablets containing the reagents were not so effective in the mouth, but might be expected from their slow solution to have a more continuous effect on the throat. For the prevention of *post operative scarlet fever in a throat and nose department* the simple measure was instituted of all patients as a routine using a mouth wash and gargle of watery acriflavine 1 in 5000 twice a day (Young and Charters, 1940). This was started immediately on admission and continued throughout the stay in hospital and there was no other change in procedure beyond this. Before its introduction one of the throat, nose and ear wards had been closed thirteen times during the preceding winter owing to outbreaks of scarlet fever and this was by no means an exceptional occurrence but since its adoption the two wards had a ^{ptal} of only five cases of post-operative scarlet fever in six years.

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CHAPTER XVII

METALLIC COMPOUNDS

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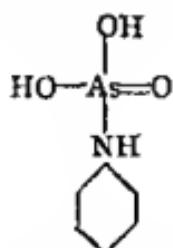
CHAPTER XVII

METALLIC COMPOUNDS

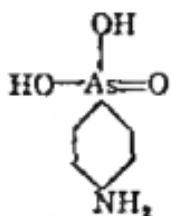
IN the specific treatment of parasitic infections chemotherapy uses three types of drugs. Some, such as extract of male fern, are galenical preparations of crude vegetable substances, others, such as emetine and the cinchona alkaloids, are pure chemicals isolated from crude vegetable substances, and the third class comprises synthetic compounds prepared in the laboratory. Among these synthetic compounds are many organo metallic substances which owe their chemotherapeutic activity to the fact that they contain metallic radicals. Despite the large number of such metal-containing compounds synthesized, there are still only five metals which play an important part in chemotherapy. These metals are arsenic, antimony, mercury, bismuth, and gold. Arsenic and antimony were well known to the Romans but their primary uses were as poisons, and physicians received them directly from the hands of magicians and sorcerers. The Arabian physicians used antimony and arsenious oxide, and Rhazes (Abu Bakr Muhammed ibn Zakaruja, 850-923) studied the toxic effects of mercury in monkeys. Mercury (grey salve) and corrosive sublimate were especially valued in the treatment of skin diseases. From the Arabs the alchemists acquired a knowledge of the medicinal uses of antimony, mercury and gold in the form of tinctures and elixirs, as is seen in that curious work "Triumphwagen des Antimonii," which, whatever its true date, almost certainly contains portions of fifteenth-century writings. The strongest advocate of the medicinal use of metallic preparations was, however, Theophrastus Bombastus von Hohenheim (1493-1541), the self-styled Paracelsus, who could write "Experience has shown that mercury is the sovereign and only remedy for the cure of all ulcers tainted with the great pox."

ARSENICAL PREPARATIONS

The first use of a metallic preparation in a known parasitic infection is due to Bruce (1895), who tested the use of inorganic arsenicals in infections due to *Trypanosoma brucei*, the causal agent of nagana in cattle. "It appears however," he said, "that arsenic has a specific action causing the haematozoa to disappear from the blood, to hinder or prevent blood destruction and emaciation and to modify the temperature chart. Whether this drug will completely cure the disease or not remains to be seen." With the further observations of Lingard (1899) on surra and the experimental observations of Laveran and Mesnil (1902), it was found that the use of inorganic arsenicals in trypanosome infections was often followed by relapses, and that the trypanosomes frequently became resistant. In 1905, however, Thomas showed that an organic arsenical compound atoxyl, was capable of definite curative action in laboratory animals infected with a number of different species of trypanosomes. This result was of particular importance since Ehrlich and Shiga (1904) had just found that atoxyl was quite inactive against trypanosomes *in vitro*. The first step in explaining the cause of this discrepancy was a reinvestigation of the structure of atoxyl. When first discovered in 1863 by Béchamp, atoxyl was thought to be the anilide of arsenic acid, but observations by Ehrlich and Bertheim (1907) showed that in reality it was *para* aminophenylarsonic acid.



Atoxyl after Béchamp



Atoxyl after Ehrlich and Bertheim

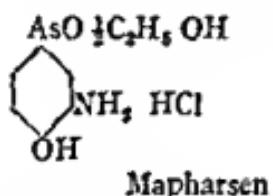
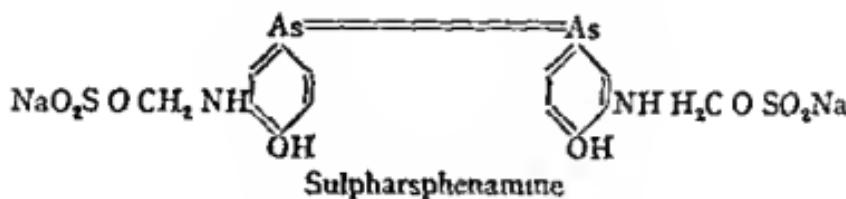
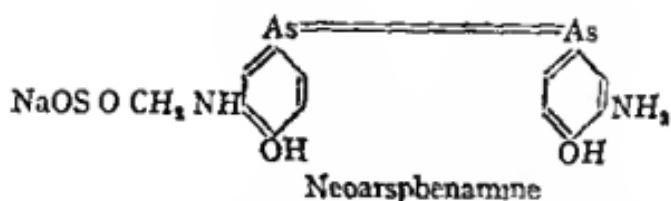
Further light on the difference between the trypanocidal activity of the arsenic acids *in vivo* and *in vitro* was shed by the discovery that the arsenoxides are active against trypanosomes *in vitro*. Ehrlich (1909) therefore thought that the

tissues must have the power of reducing the quinquevalent arsionic acids to the tervalent arsenoxides which then destroy the trypanosomes. An intensive study of the tervalent organic arsenicals was therefore undertaken. It was found that reduction of the quinquevalent phenylglycine-*para* arsionic acid with sodium hyposulphite resulted in a tervalent compound, *para*-arsenophenylglycine. This substance, in which the two arsenic atoms are linked by a double bond and each is coupled to the benzene nucleus by a single linkage, represents the arsenobenzene type of organic arsenical and is therefore the precursor of the arsphenamine compounds which have played so large a part in the chemotherapy of spirochaetal infections. Nevertheless, although the tervalent arsenicals have proved of value in syphilis, in sleeping sickness they have not been so successful. Early attempts by Koch (1907) and others to treat African sleeping sickness with atoxyl showed that, although apparent cures were produced, relapses were not uncommon and optic atrophy was a not unusual sequel. Other quinquevalent arsenicals have therefore been evolved. From the original observations of Bruce there have thus developed two types of organic arsenicals, the tervalent and quinquevalent compounds.

TERVALENT ARSENICAL COMPOUNDS

The first of the arsenobenzene derivatives to be used in the treatment of human syphilis was arsphenamine (Ehrlich and Hata, 1911), which contains both amino- and hydroxy-groups in the benzene nucleus. The toxicity of arsphenamine, however, is such that a further search for allied compounds was undertaken, and neoarsphenamine, sulpharsphenamine, and silver arsphenamine are now used in its place. The two former are official preparations of the *British Pharmacopœia* of 1932. The latter is but rarely used.





Ehrlich's original conception of the ideal chemotherapeutic agent was of a drug which would eradicate the parasites as the result of a single dose—a *therapia magna sterilisans*. In relapsing fever the arsphenamines play such a part, since one or two injections are enough to destroy the spirochaetes and bring the disease to an end. So far as the spirochaetes of syphilis are concerned, however, the *therapia magna sterilisans* has not yet been obtained, for it is now believed to be essential to combine the administration of the arsenical preparation with a compound of a heavy metal, either mercury or bismuth. In America the most usual plan is to adopt what is known as continuous treatment, alternate courses of arsenic and bismuth being given over a period of fifty-six weeks. In Great Britain and on some parts of the continent the usual rule in primary cases is to administer the arsenical and the bismuth or mercury derivative at the same time, alternating with short periods during which no drug is given, the whole treatment occupying ninety weeks.

Recently, however, claims have been made for the continuous administration of arsphenamine by the drip method in primary and secondary syphilis. Hyman, Chargin, and

Leifer (1939), for instance, gave a total of 4 gm of neoarsphenamine in five days, 1 gm being given in 1,500 c cm of a 5 per cent solution of dextrose in fifteen hours. Of fifteen patients thus treated, eleven had a negative blood Wassermann five years later, and two other patients had become reinfected.

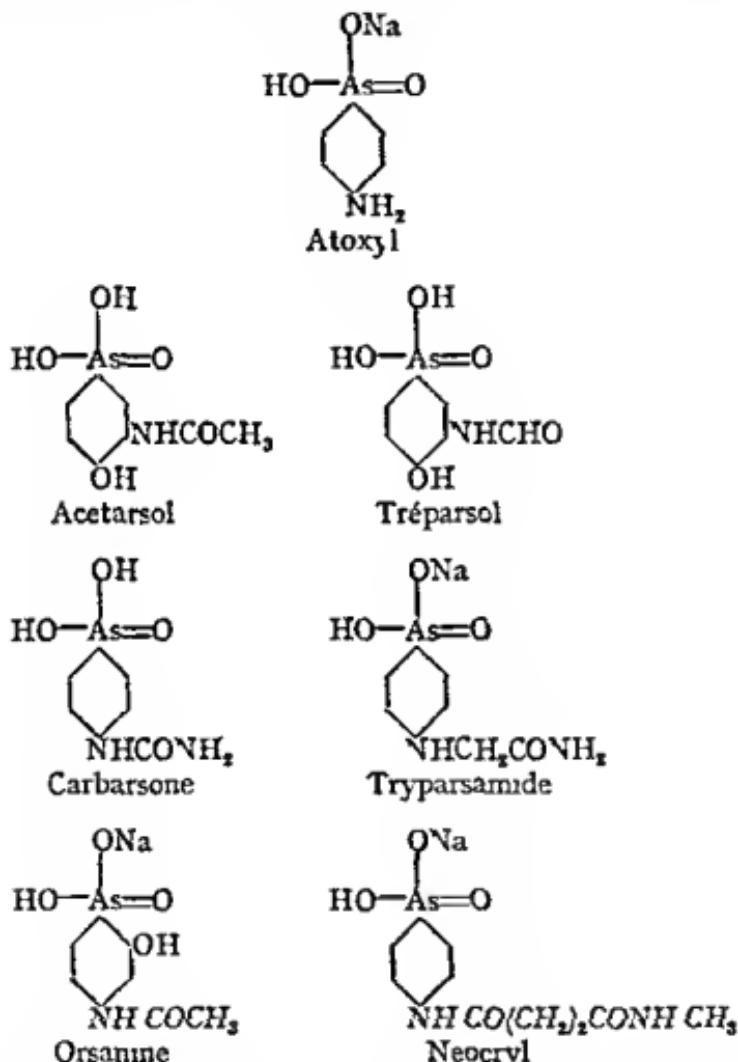
During the past few years, a number of other tervalent arsenical preparations have been introduced in the chemotherapy of syphilis. Trisodarsen, a derivative of sulpharsphenamine and thioarsene, disodium bis (β -sulphophenyl)-acetamidophenylthioarsinite, would seem to have no advantages over neoarsphenamine, but mapharsen or arsenoxide, the hemialcoholate of 3-amino-4-hydroxy-phenylarsenous oxide hydrochloride, has some claims to note, since it is claimed that with a smaller dose of arsenic it produces a therapeutic effect equal to that of the arsphenamines, is more readily tolerated, and is less toxic to the liver.

Apart from their action in syphilis, yaws and relapsing fever, the tervalent arsenicals have proved of value in Vincent's angina and in sodoku or rat-bite fever due to *Spirillum minus*. No bacterial infection in man appears to benefit from tervalent arsenicals with the possible exception of cutaneous anthrax, in which condition Louw and Pijper (1922) obtained remarkable results with neoarsphenamine. Although neoarsphenamine has little or no curative action on experimental anthrax infections in mice, its curative effect in man has been confirmed by Eurich (1933), Spencer (1934), and Gilbert (1935). Recently Rosenthal and Elvove (1939) have found that the tervalent derivatives of 4-nitro-4'-amino-diphenyl-arsinic acid are active in curing streptococcal infections in mice. In certain diseases due to pleuro-pneumonia-like organisms, such as agalactia of sheep and pleuro-pneumonia of cattle, the tervalent arsenicals have also been found to have a curative action, but in protozoal infections, such as trypanosomiasis, amoebiasis, and malaria, they are of little value apart from a non-specific tonic effect. In protozoal diseases quinquevalent arsenicals are of greater importance.

QUINQUEVALENT ARSENICAL COMPOUNDS

In order to overcome the disadvantages of atoxyl, a number of other quinquevalent arsenicals have been prepared. The most important of these are acetarsol, tryparsamide, carbarsone, orsanine, tréparsol, and neocryl. The chemical relationship of these compounds to atoxyl and to one another is shown on page 227. Although in many ways less toxic than the tervalent arsenicals, all members of this group have to a greater or less degree a tendency to produce optic atrophy. On the other hand, they penetrate more readily than the arsphenamines into the cerebrospinal fluid and are therefore of special importance in the treatment of parasitic infections of the central nervous system. Thus tryparsamide (tryparsone), the sodium salt of N-phenylglycine-amide-*p*-arsonate, first prepared by Jacobs and Heidelberger (1919), is of special value in neurosyphilis and in the treatment of the secondary stages of sleeping sickness in man, when once the trypanosomes have invaded the brain. Unfortunately, in this latter condition it is often necessary, in order to bring about cure, to give such large doses that optic atrophy is by no means rare. Acetarsol (acetarsone, stovarsol, spirocid), 3-acetyl amino-4-hydroxyphenyl arsionic acid, was originally prepared by Ehrlich and Hata (1911) and is now used in the treatment of amœbic dysentery, syphilis, yaws, relapsing fever, and malaria. In amœbic dysentery it causes a rapid disappearance of the clinical symptoms but relapses are common and reactions, especially dermatitis, are not uncommon. The frequency of toxic reactions in fact militates against its use in congenital syphilites in whom otherwise it would be of value, since, unlike the arsphenamines, it can be given by mouth. Tréparsol, 3-formylamino-4-hydroxyphenylarsonic acid, and orsanine, the sodium salt of 4-acetylamino-2-hydroxyphenyl-arsionic acid are used, chiefly in the French African colonies, in the treatment of human trypanosomiasis. The latter compound, unlike tryparsamide, is said to be effective in all stages of sleeping sickness. Neocryl, sodium succinamido-methylamide-*p*-arsenate, prepared by Morgan and Walton (1931), has been found

to be active both in trypanosomiasis and in syphilis. The clinical results obtained by Murgatroyd (1937) in the treatment of sleeping sickness were, however, not more favourable than those following tryparsamide therapy.



Carbarson, 4-carbamidophenylarsonic acid, although first prepared in 1909 by Ehrlich and Bertheim, was not thoroughly investigated until 1931, when David Anderson, Koch, and Leake found that *in vitro* it killed *Entamoeba histolytica* in a dilution of 1 in 4,000. Later Reed and his colleagues (1932)

showed that of 175 persons with amoebiasis, only four continued to show the presence of amoebæ in the stools after a single course of treatment consisting, for the average adult, of 0.25 gm by mouth twice daily for ten days. Although in the treatment of amoebic dysentery carbarsone is second only in importance to emetine and unlike emetine has a tonic action, it is useless in the treatment of amoebic hepatitis.

ANTIMONY COMPOUNDS

The chemotherapeutic use of antimony dates from the discovery by Broden and Rodhain (1906) that potassium antimonyl tartrate, tartar emetic can be safely injected intravenously. Although in African sleeping sickness tartar emetic is without action, Plummer and Thompson (1908) found that the blood of laboratory animals infected with *Trypanosoma brucei* or *T. evansi* is sterilized by injection of tartar emetic. Since then tartar emetic has been widely used in cattle in the treatment of infections due to *T. vivax* and *T. congolense*. Horses suffering from *T. evansi* and cattle with *T. brucei* infections are also benefited by tartar emetic.

In man, the chief use of tartar emetic has been in the treatment of schistosomiasis, and in Egypt many thousands of persons suffering from *Schistosomum haematobium* infections have been successfully treated. Unfortunately, owing to the toxicity of tartar emetic, various attempts have had to be made to find less toxic preparations of antimony. As in the case of arsenic these less toxic compounds include both ter- and quinquevalent antimony derivatives. The most important of the tervalent preparations is fouadin which is an antimony compound of pyrocatechol sodium disulphonate. The standard course consists of the injection on the first day of 1.5 c cm of a 7 per cent solution of fouadin, on the second day 3.5 c cm, and on the third day, and subsequently three times a week, 5 c cm to a total of 40 c cm. 5 c cm of the solution contains 42.5 mgm of antimony. About 33 per cent of cases relapse. In infections due to *S. japonicum*, fouadin although it causes fewer reactions, is less efficient than tartar emetic. Unfortunately the less toxic quinquevalent antimonials are

quite ineffective in treating schistosome infections. The quinquevalent antimony compounds are for the most part derived from phenylstibonic acid, which was first successfully synthesized by Schmidt (1920). Of these quinquevalent compounds which have completely revolutionized the treatment of kala-azar or visceral leishmaniasis, the most important are neostam, urea stibamine, neostibosan and, more recently, solustibosan, which is said to be a hexonic acid derivative containing quinquevalent antimony. From a death rate in India of approximately 20 per cent, following the use of tartar emetic, the death rate of kala-azar treated with quinquevalent antimony derivatives has been reduced to under 5 per cent. Antimony, whether in the ter- or quinquevalent form, has not proved effective in the treatment of oriental sore. In the comparatively rare disease known as granuloma inguinale, tartar emetic or tervalent antimony compounds, such as sodium antimony thioglycollate, appear to have a curative action. In lymphogranuloma venereum antimony derivatives are of less value than drugs of the sulphonamide series.

MERCURY COMPOUNDS

Although mercury was at one period universally used in the treatment of syphilis the general consensus of opinion now agrees that it is of less value, when used with arsenic, than bismuth. A number of organic mercurial compounds, however, have been tested for their action in septicaemia and on localized bacterial infections. The most important of these compounds are metaphen, the anhydride of 4-nitro-5-hydroxy-mercuri-2-cresol: mercuophen, hydroxymercuri-ortho-nitrophenolate and mercurochrome-220 soluble, disodium dibromo-hydroxymercuri-fluorescein. In the treatment of streptococcal and pneumococcal infections these organic mercurials are far inferior to the sulphonamide derivatives: this failure is due to the fact that any killing action they possess is due to the presence of free unbound mercury in excess of the mercury irreversibly bound by the serum proteins. The organic mercury compounds would thus appear to act merely as a reservoir of an ionizable form of mercury.

BISMUTH COMPOUNDS

Fifty years ago Balzar (1889) suggested the use of bismuth in the treatment of syphilis, but no experimental observations were made until 1916, when Robert and Sauton found that fowl spirochaetosis is rapidly cured by bismuth salts. These observations, in the stress of war, passed unnoticed, and it was not until 1921 that Sazerac and Levaditi showed that bismuth was active in curing both experimental syphilis in the rabbit and the actual disease in man. A vast number of bismuth compounds have now been prepared as anti syphilitics, varying in bismuth content from 4 to 98 per cent. The chemotherapeutic activity of any compound depends, however, less on its metallic content than on its rate of absorption, rate of excretion, and powers of penetration. At present there is a tendency to prefer fat soluble preparations to colloidal, water-soluble or water insoluble derivatives. Whatever preparation of bismuth is used it should be emphasized that bismuth alone is incapable of completely curing syphilis. The practice of giving bismuth only originally carried out in France, led to a high percentage of relapses. In yaws, however, bismuth alone has given most striking results, and owing to its cheapness and absence of toxicity is probably the ideal drug for mass treatment when the aim is not so much to eradicate the infection in every case as to prevent the individual from being a source of infection. In the experimental treatment of leptospiral jaundice in the guinea-pig bismuth preparations have shown considerable activity in leptospiral infections in man, however, their value is less than that of immune serum.

GOLD COMPOUNDS

Gold was used in early Roman and Indian medicine. Its modern use dates from the finding by Koch (1890) that the double cyanide of gold and potassium has a lethal action on tubercle bacilli *in vitro*, although *in vivo* it is inactive. Later Møllgaard (1924) introduced under the name of "sano-crysin" the double thiosulphate of gold and sodium originally prepared in 1845 and a large number of organic gold prepara-

tions have also been recommended for the treatment of human tuberculosis. It is now believed that these gold salts have no specific action on the tubercle bacillus. When any benefit follows their use and in certain cases with recent exudative lesions such improvement appears to be undoubted, it must be put down to a stimulation of the defence mechanism of the body. Certain Japanese workers believe that the value of the gold preparations lies not in their gold content but in the sulphhydryl group which they contain. Gold salts are also of value in cases of rheumatoid arthritis which, although of unknown etiology, appear to be due to an infection. It must, however, be remembered that the margin between therapeutic action and toxicity is extremely small.

OTHER METALLIC COMPOUNDS

Although so few metals have found an established place in chemotherapy, the action of many others has been tested. Thus, both copper and cadmium have, it is claimed, some beneficial action in tuberculosis in man. Tellurium, vanadium, platinum, thorium, strontium, indium, gallium, gold, rhodium, and ruthenium have all been found to be spirochaetocidal in experimental animals, but to have little or no action in man. Rhodium cures a small percentage of guinea-pigs suffering from leptospiral jaundice and copper, in the form of a cupro-oxyquinoline disulphonate has been recommended in malaria.

The reasons why so small a number of metals are active in the destruction of parasites is still unknown. The spirochaetocidal action of arsenic, mercury, and bismuth appears to be intimately connected with their action on the sulphhydryl groups present in the spirochaetes but, despite the practical triumphs of chemotherapy, the theoretical basis of the science is only now being slowly and painfully disclosed.

The main practical lesson to be derived from a study of the chemotherapeutic treatment of infectious diseases with metallic compounds is, however, the importance of giving the drugs for short periods only, but in doses as large as can be tolerated. Otherwise, there is every possibility that the parasites instead

of succumbing will become drug-resistant, and the last state of the patient will be worse than the first

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CHAPTER XVIII

CALCIUM

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CHAPTER XVIII

CALCIUM

THE therapeutic uses of calcium may be divided into four groups (1) To make good deficiencies in the supply stored in the bones, (2) to raise the serum calcium level, (3) to act as an antacid, and (4) for other less clearly defined purposes. The first two are by far the most important. An intelligent appreciation of the place of calcium in therapeutics necessitates a brief consideration of its metabolism and functions in the animal body. Lime and iron are the two minerals which are likely to be deficient in the dietary of man. Both occupy important positions in the body economy especially during periods of growth. Normal growth indeed is largely dependent on the orderly absorption and retention of lime. Although it is true that increase in height can and does proceed even when the supply of calcium is defective, the skeleton in this circumstance lacks strength. Although most, indeed almost all of the lime is contained in the bones, this store must not be regarded as a dump but rather as a mobile reserve capable of responding to the calls of other tissues. The accumulation of calcium in the skeleton depends on the relative needs of the various tissues and the amount available from the food. In the body fluids and soft tissues calcium is of vital importance in the control of neuro muscular excitability, it plays an essential part in the maintenance of acid base equilibrium and in the regulation of cellular permeability, and it is indispensable for the coagulation of blood and the clotting of milk.

DEFECTIVE RETENTION

The first indication for calcium therapy is any condition associated with defective retention of this element. In the human subject this is generally due to one or more of three causes (1) Insufficient intake of lime in the food (2) insufficient

vitamin D, and (3) presence of acidosis. The adult male requirement of calcium is about 0.6 grammes, which is the amount contained in half a litre of milk. This must be increased during any period in which active growth is taking place, namely, childhood, adolescence, and during pregnancy. Infants receive enough lime unless they are given milk which has been over-diluted, children require the equivalent in calcium of at least one quart of milk, expectant mothers should receive this amount in addition to a good mixed diet. The most natural and the best method of supplying lime is undoubtedly in the form of milk or milk products, since these contain valuable food materials in addition to calcium. For those unfortunate individuals who cannot tolerate milk, it may be necessary to supply the lime in other form such as a soya-bean mixture enriched with calcium salts. Stearns recommends a mixture of soya-bean flour containing 4.7 per cent calciumdiphosphate. Vegetables, despite what has been written about them, are not satisfactory sources of lime. Occasionally, as in fat dyspepsia or coeliac disease, the presence of excess of fatty acid in the bowel prevents the adequate absorption of calcium. In such a case it is wise to supply milk poor in fat in the form of skimmed milk and this may be obtained as a dry powder, e.g. Cow and Gate separated milk food (white label) or prolac (G.L.).

To ensure adequate retention of calcium even when present in abundance in the food the ingestion of a sufficiency of vitamin D is essential. For the adult a good mixed diet containing animal fat is all that is necessary because exposure to daylight will lead to the formation of sufficient vitamin D in the skin. Infants and children, especially those reared in the smoky atmosphere of industrial areas, require more than this, and cod-liver oil is probably the best and cheapest preparation for the purpose. Vitamin D concentrates may, however, be used and, for patients with an intolerance for fat, exposure to ultra-violet radiation is valuable.

SKELETAL DEFICIENCY

The conditions in which the skeleton contains too little

calcium will now be considered. Osteoporosis in the adult is generally the result of defective intake of lime occasionally associated with an insufficient supply of vitamin D. Rickets in the child and osteomalacia in the adolescent and adult are conditions in which there is a vitamin D lack often with a poor intake of calcium. The use of vitamin D and calcium in these conditions is obvious all that needs emphasis is the importance of early diagnosis and the supply of ample vitamin D and lime, the latter most effectively in the form of milk and milk products, if calcium salts are used the lactate or gluconate may be given in doses of 120 grains or more three times daily.

There are, however, osteoporotic states in which neither calcium nor vitamin D are deficient. Clearly any attempt to cure such conditions by the use of these substances is doomed to failure and likely to cast discredit on this form of therapy. Decalcification of bones is common in osteogenesis imperfecta, in generalized osteitis fibrocystica and in disuse atrophy of a limb, but in none of these conditions will calcium and vitamin D therapy lead to any improvement unless and until the underlying cause is satisfactorily dealt with. There is no satisfactory evidence that calcium with or without vitamin D accelerates the rate of healing in fractures.

LEAD POISONING

Calcium is of the utmost value in the prevention and treatment of lead poisoning. It has been conclusively shown that a diet specially high in lime is an excellent prophylactic. The use of calcium in the prevention and treatment of lead poisoning is based on two facts, (1) that the deposition of lead in the skeleton is favoured by increased retention of lime, and its elimination is accelerated by anything causing decalcification, and (2) that calcium has a sedative effect on the spasm of visceral muscle. It has been found that a diet specially high in lime is an excellent prophylactic against lead poisoning. Workers using lead should receive at least three pints of milk every day and may with advantage be given even more.

calcium In the acute stage of lead poisoning, and especially in the presence of lead colic, anaemia and nervous manifestations, such as encephalopathy or paralysis, the administration of large amounts of lime should begin immediately a high-calcium diet, containing at least three pints of milk, together with cheese, milk puddings, eggs, and green vegetables should be given In addition, calcium lactate or gluconate may be prescribed when the patient is suffering from colic A slow intravenous injection of 20 c.c.m. of 10 per cent calcium gluconate is often effective in relieving pain, this dose may be repeated in four hours if there is a return of intestinal spasm In practice calcium therapy is supplemented by the occasional use of morphine Even after the acute symptoms have been relieved, it is necessary to ensure a maximum storage of lime by the administration of milk fortified with calcium gluconate This measure is intended to remove the lead from the blood and fix it in the bones in the shortest possible time When the patient has been on this regime for a week and is free of all acute symptoms, an effort should be made to promote the excretion of the stored lead by the administration of a lime-poor diet and some acid producing substance, such as ammonium chloride (30 grains four-hourly) or dilute hydrochloric acid (60 minims four-hourly) The food should not contain milk, milk products, eggs or green vegetables but may include meat, cereals, tomatoes and apples Instead of or in addition to, ammonium chloride, intramuscular injections of parathyroid extract (30 to 50 units) may be given daily Caution is necessary in the removal of lead from the bones for if it is done too rapidly an attack of acute poisoning may be precipitated Accordingly "de-leading" measures should be carried out for periods of four days with intervals of three days

MAINTENANCE OF THE SERUM CALCIUM AT THE NORMAL LEVEL

The accepted limits of normality for the serum calcium are 9 to 11 mgm. per cent It may be mentioned that the value for serum calcium gives no indication either of the amount already

stored in the body or the quantity being retained or lost at the time of examination. The level of serum calcium depends upon the balance struck between absorption, excretion and deposition in the bones. At present three factors are known, each of which tends to increase the concentration of calcium in the blood, namely, vitamin D, parathyroid hormone, and the presence of excess acid in the tissue fluids. Vitamin D facilitates the absorption of lime whereas parathyroid hormone increases the amount of lime which is continuously being released from the bones. Excess of acid radicle may also raise the serum calcium by promoting the decalcification of bone. Its chief effect, however, is to increase the proportion of ionized calcium in the blood. In this connexion it is helpful to make use of the hypothesis that calcium exists in the body fluids in an ionized and in a non-ionized form, and that the former is the active fraction responsible for the regulation of neuro-muscular excitability. The use of this assumption is illustrated by a consideration of the treatment of tetany. Clinical varieties of tetany are conveniently divided into two groups according as the serum calcium is or is not reduced. In the first or hypocalcaemic group are included cases associated with rickets, coeliac disease, renal dysfunction and hypoparathyroidism. In the latter or eucalcæmic group fall gastric, bicarbonate and hyperventilation tetany, all associated with alkalosis. Using the hypothesis that ionized calcium is the active fraction, it is obvious that in the eucalcæmic group there is a diminution in the amount of ionized calcium caused by a shift in acid base equilibrium to the alkaline side. In the hypocalcaemic group the proportion of ionized to non-ionized calcium may be normal although the actual concentration of the ionized fraction is low owing to the great fall in total calcium. This has a practical bearing on therapeutics. In the hypocalcaemic it is usually sufficient to raise the total calcium concentration of the blood, whereas in the eucalcæmic type of case it is advisable to render the blood less alkaline.

The level of serum calcium can be raised in one of four ways. (1) By the parenteral administration of a suitable calcium salt, (2) by the injection of parathyroid extract, (3)

by the administration of an acid producing salt, and (4) by the administration of vitamin D with a diet rich in lime. Parenteral administration of calcium especially if done by the intravenous route, provides the most rapid method of raising the serum calcium level. It has, however, but a transient effect and is therefore suited especially for the tiding over of an emergency, such as a prolonged convulsion. It should be noted that if the tetany is of the eucalcæmic variety the beneficial effect of the increase in serum calcium may be almost immediately vitiated by the fact that little addition is made to the ionized fraction. 10 to 20 c cm of a 20 per cent solution of calcium gluconate should be slowly injected into one of the veins, five minutes being allowed for the injection. Immediately afterwards a similar amount may be given by the intramuscular route. The intravenous injection causes an almost instantaneous disappearance of the symptoms of tetany, and the intramuscular administration helps to prolong this effect. 10 c cm of a 10 per cent solution of calcium levulinate or calcium chloride may be used in place of the gluconate, but care must be taken with injection of the chloride as it is apt to be irritating to the soft tissues. If the patient is receiving digitalis, calcium salts should not be given intravenously, since an additive effect may be produced with disastrous results.

The administration of parathyroid extract would appear to be the ideal method of treatment when the secretion of the parathyroid hormone is deficient, e.g. after extirpation of the parathyroid glands during thyroidectomy and in cases of idiopathic hypoparathyroidism. Even in this type of case there are disadvantages—the preparation is expensive and with prolonged use of the extract habituation occurs so that larger doses have to be employed with less and less effect. In cases of tetany associated with defective retention of lime the use of this expensive preparation is neither necessary nor desirable, since it produces its effect on serum calcium by decalcifying the osseous tissue. The ideal indication for the use of parathyroid preparations is the appearance of signs of latent tetany after the operation of thyroidectomy or removal of a parathyroid adenoma. If acute tetany supervenes, the intravenous adminis-

tration of a calcium salt is to be preferred, since injection of parathyroid extract does not produce a significant elevation of serum calcium in less than six hours. The dose and route of administration vary with the severity of the manifestation. Oral administration is useless as a method of raising serum calcium, in the more severe type of case 30 units of one of the recognized preparations should be given intravenously, followed in six hours by an intramuscular injection of the same amount and thereafter the dose regulated by clinical and biochemical considerations. In mild cases 20 units intramuscularly usually suffice as an initial dose. It is essential whenever parathyroid therapy is undertaken to control its use by serial estimation of the serum calcium, which should not be allowed to exceed 13 mgm per cent. When hypercalcæmia is produced signs of listlessness appear and, if unchecked, coma may result. If these symptoms should occur, the administration of parathyroid must be stopped and an intravenous injection of normal saline given in order to reduce the high viscosity of the blood produced by the hypercalcæmia and to accelerate the blood flow.

The oral administration of ammonium or calcium chloride (both being acid producing salts) or dilute hydrochloric acid, is a simple and effective way of raising serum calcium. This is achieved by increasing the amount of lime released from the bones. As a form of therapy it is specially indicated whenever there is a tendency to alkalosis (insufficient acid radicle in the body fluids). Ammonium chloride or calcium chloride (15 to 30 grains) may be given six times daily, and hydrochloric acid should be given as an $\frac{1}{2}$ solution in amounts of 50 to 100 c cm per day. The chief action of all these substances is to supply calcium to the blood from the bones. It should be emphasized that little of the lime from calcium chloride is actually absorbed. The one risk associated with the use of these acid-producing substances is the development of acidosis. This is almost negligible when there is no underlying disturbance of acid-base equilibrium, but with infants and young children who are prone to suffer with intestinal disorders and in patients with chronic interstitial nephritis great care must be

taken to watch for the initial manifestations of acidosis. Diarrhoea and rapid breathing are indications for immediately stopping this form of treatment. In any case it is advisable not to continue the administration of ammonium or calcium chloride to an infant or child with tetany for longer than three days. When as in post-operative tetany, it is desired to give acid producing substances for long periods, it is essential to make certain that there is an ample supply of calcium in the food in order to prevent a progressive osteoporosis.

GASTRO-INTESTINAL DISORDERS

Calcium carbonate is useful as an antacid. Suspended in water it is neutral in reaction, it has little effect on the bowel except to increase the bulk of the stool and in excess it coats and protects any ulcerated regions. It is best given in tablets which readily disintegrate in water, since the dry powder being easily inhaled may lead to painful spasms of coughing. In the treatment of peptic ulceration it is often given with oil of cinnamon (calc. carb. 10 grains, oil of cinnamon $\frac{1}{2}$ minum) which acts as a flavouring agent and carminative.

Calcium carbonate is also an ingredient in many prescriptions used for the treatment of diarrhoeal conditions. The beneficial effect is produced mainly by the neutralization of the irritating organic acids formed in the bowel but it is possible that there is a direct sedative action on the intestinal wall with a decrease in the cellular secretions. Other calcium salts, such as the lactate or gluconate are said to be of value in ulcerative colitis.

RENAL CONDITIONS

In chronic interstitial nephritis alkali is acknowledged to be the most important therapeutic agent. Recent investigations have shown that the administration of calcium salts may improve renal function quite considerably. When there are symptoms of tetany, intramuscular injection of 10 c.c.m. of 10 per cent calcium gluconate may be of great help in alleviating the condition. In pyogenic infections of the urinary tract calcium or ammonium chloride (15 to 30 grains four-hourly) is

often given in order to render the urine acid during mandelic acid or hexamine therapy. It is essential in this connexion that the urinary pH should be frequently estimated and kept below 5.5.

CHILBLAINS, URTICARIA, AND ALLERGIC CONDITIONS

The use of calcium salts has been recommended for the diminution of localized inflammatory processes and for accelerating the removal of effusions. Clinically, however, the results are disappointing and the apparent successes are commonly attributed to factors other than calcium. More satisfactory is the evidence favouring the use of lime in the treatment of chilblains, presumably the underlying effect is a decreased permeability of the capillary endothelium. Large doses of calcium salts are required either the lactate or gluconate may be used, but it is advisable, unless there is any special contraindication, to increase the intake of milk or milk-products. In adults on a good mixed diet it is rarely necessary to supply vitamin D in special form. Although in many cases calcium therapy is likely to prove disappointing, it is well worth a trial as some almost dramatic recoveries are encountered. Urticular conditions, angioneurotic oedema, and hay-fever may also respond well to administration of lime salts. 10 c.c.m. of 10 per cent calcium gluconate intravenously followed by 10 c.c.m. of a 10 per cent solution intramuscularly appears to have a beneficial effect on the rash of serum sickness, but little if any on the joint pains. For the other allergic manifestations, such as asthma, calcium salts are of little value.

HÆMORRHAGIC CONDITIONS

It is well known that the presence of calcium ions is essential for the coagulation of the blood. On this basis calcium salts are frequently used in hæmorrhagic conditions or when loss of blood from capillary oozing is feared. Oral or parenteral administration of calcium is almost a routine procedure prior to surgical measures on a patient with jaundice. It is difficult to see the rationale of this form of therapy since serum calcium

is rarely if ever reduced in icteric patients. It may be that the presence of bile pigment in the blood inactivates some of the calcium ions so that there is an insufficiency of active calcium for effective blood coagulation. In purpuric states the administration of lime may be of value but only when there is evidence of increased capillary permeability, such as urticaria or oedema. In haemophilia calcium therapy is useless.

TOXIC CONDITIONS

There is some experimental evidence that calcium has a protective action on the liver. It would therefore seem that its use is worth a trial in conditions of toxic hepatitis. Some indeed recommend its administration in all cases of toxæmia known to be non-bacterial in origin, but the evidence in favour of this procedure is not convincing.

CARDIAC DECOMPENSATION

For some years past calcium has been used in the treatment of cardiac failure. It apparently has a stimulating effect on the vagal centres and strengthens the heart beat. Great caution, however, must be observed and it should not be given to a patient actually receiving digitalis. Further work will require to be done before the place of calcium in the treatment of heart failure is definitely determined. Meanwhile, it is right to consider its use in patients with cardiac decompensation when the rhythm is regular and digitalis has not proved successful. The patient should not have received any of the digitalis drugs for at least four days previously. 10 c.c.m. of 10 per cent gluconate may then be given intravenously once or twice daily.

TUBERCULOSIS

Many attempts have been made to prove that calcium therapy, with and without the addition of vitamin D, is beneficial in pulmonary and other forms of tuberculosis. It is unlikely that the process of calcification in tuberculous lesions is the same as in healthy bone so that, although an ample supply of lime is clearly an advantage, it is doubtful if high retention

of this element does anything to promote its deposition in tuberculous areas. Carefully controlled investigations have so far failed to reveal satisfactory evidence of an acceleration of the healing process by the administration of calcium and vitamin D.

PREPARATIONS OF CALCIUM

When it is desired to increase the intestinal absorption of lime calcium gluconate or calcium sodium lactate are probably the best salts. Although it is stated that the insoluble carbonate and phosphate are converted into soluble salts in the alimentary tract most practitioners restrict their use to the treatment of local conditions in the bowel. Calcium gluconate which contains 9.3 per cent of calcium is an odourless, tasteless, non irritant salt with a low solubility in water. It is generally given in powder or tablet form in doses of 75 grains.

The use of calcium chloride should be restricted to those conditions in which it is desired (1) to raise the serum calcium and more especially to increase the proportion of ionized calcium and (2) to increase the acidity (i.e. to decrease the pH) of the urine. It may be given in doses of 15 to 30 grains four-hourly, but prolonged administration is inadvisable in view of the possibility of acidosis, for the manifestations of which a careful watch should always be kept.

For intravenous or intramuscular administration 10 or 20 per cent gluconate or 10 to 15 per cent levulinate should be used. Great care must be exercised that the rate of injection into the vein is not too rapid, because of the possible action on the vagus mechanism and the heart muscle. The chloride of calcium is an irritating salt and should be avoided if possible, even for intravenous injections, since a small amount leaking into the perivascular tissues may cause considerable pain and sloughing. When intestinal absorption is faulty and an immediate effect on the serum calcium is not required intramuscular administration of 10 per cent calcium gluconate or levulinate may be used. Subcutaneous injections of calcium preparations are of little value since a reasonable amount can not be given by this route. For the same reason colloidal

preparations are of little therapeutic value. There are many preparations of calcium carbonate available for the treatment of diarrhoeal conditions. The B P C preparations *Mist cretæ* ($\frac{1}{2}$ to 1 ounce) and *Mist cretæ composite* in doses of 1 ounce (containing 3 minims of tincture of opium) for an adult, 120 minims for a child of seven years, are probably as good as any. It may be given in powder form as the *Pulvis cretæ aromaticus* (B P) in doses of 10 to 60 grains.

CHAPTER XIX

IRON

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CHAPTER XIX

IRON

THE present position of iron in therapeutics rests partly on scientific knowledge and partly on empiricism, and rarity of toxic manifestations, even with the use of large doses, makes its empirical employment as a tonic, or in undiagnosed cases, a safe procedure. None the less, the evidence now available about the effect of iron in many forms of anaemia has increased the confidence with which it is prescribed and has brought into being a diagnostic check, in that failure of the patient to respond, when it was confidently expected that he would do so, throws doubt upon the accuracy of the diagnosis or suggests the presence of complicating factors interfering with iron absorption or haematopoiesis. The characteristic features of the blood in patients who will benefit by iron administration at all ages and in various syndromes are such that a group of anaemias may be recognized and referred to as the iron-deficiency anaemias, these respond to iron therapy and to no other, although it must be borne in mind that iron is of value as an adjunct to treatment in other diseases and that iron itself may sometimes produce better results if given with other drugs in cases that belong to the iron-deficiency group of anaemias.

THE MODE OF ACTION OF IRON

In health, iron is obtained from various foods, particularly meat and green vegetables, it is absorbed in the duodenum, and is probably prepared for absorption in part by the action of hydrochloric acid, it is also probably absorbed in its bivalent form. Iron excretion takes place principally through the large bowel, and in health there is a balance between absorption and excretion with the retention of adequate reserve storage, principally in the liver. As it is required for haemoglobin

formation iron is released from storage and utilized by the bone marrow for the formation of haemoglobin within the developing red cells. The major portion of the iron set free by destruction of old red cells is returned to store and again utilized for further haematopoiesis. Throughout life there are factors that may act singly or in concert to produce a depletion of the iron reserves of the body, for this reason it is to be expected that iron-deficiency anaemia will be observed at all ages.

CRITERIA OF IRON-DEFICIENCY ANAEMIA

From the clinical aspect, pallor is the sign that draws attention to anaemia, there are, however, many points in both the history and examination of a patient that will indicate the likelihood of iron deficiency as the underlying cause, proof of this must be sought in the blood, and the most important diagnostic feature of this type of anaemia is a low colour index. The red cells are pale, the mean diameter is diminished, as are also the mean cell-volume and mean haemoglobin-concentration, but the usual diagnostic essential is the disproportion in reduction between erythrocytes and haemoglobin, giving rise to the low colour-index. In the majority of cases iron therapy will prove the accuracy of the diagnosis by causing a steady return to normal of the haemoglobin and erythrocytes and a mounting of the colour index to approximate unity. The many other features that may be noted by the laboratory worker during recovery are of minor value to the clinician and need not be discussed here. It can thus be claimed that iron has a specific effect in one group of anaemias, an adjuvant effect in some other anaemias, and probably a tonic effect in a number of diseases that may be accompanied by anaemia.

IRON PREPARATIONS

The British Pharmacopœia contains a number of iron preparations, the morning post generally brings advertisements for many more. To those who believe in simplicity, cheapness, and efficiency there is no need to go beyond the official preparations. It is generally accepted that organic iron is badly

absorbed, and that ferrous iron is therapeutically more efficient than ferric iron. For adequate therapeutic effect it is essential to give iron in large doses, at least the maximal official dose and often more should be used when iron deficiency anaemia is known to exist, and at least half this dose when iron is given as an adjuvant or a tonic. Occasionally a patient who has failed to respond to oral administration will respond to intramuscular injection (e.g. *injectio ferri B.P.* 15 minims) but this is rare, more frequently the patient will complain of inability to take iron by mouth on account of its taste or the production of gastritis or enteritis, in this event a change of preparation is often effective. Iron may produce toxic symptoms when given parenterally and this method should only be used when failure to respond to iron by mouth occurs and the diagnosis of uncomplicated iron-deficiency anaemia has been confidently made.

When a patient fails to respond to iron therapy, and clinical judgement insists that there should be a response it is to be suspected that either the diagnosis is wrong or that some complicating factor, especially of a type associated with iron-deficiency anaemia, such as a bleeding ulcer or cancer of the gut, is awaiting diagnosis. The converse, however, is not true, reaction to iron may occur in the presence of such a complication, and may have the undesired effect of vicariously improving the patient's condition.

THE USE OF IRON IN VARIOUS TYPES OF ANAEMIA

The principal features observed in the blood when iron deficiency is present have been described, the clinical features are more variable. It is important to remember that iron deficiency may occur or be induced by a number of mechanisms and produce thereby a similar type of anaemia at various ages and in association with various complicating diseases, these may be considered under the following headings.

Nutritional anaemia—The frequency with which nutritional anaemia occurs in infants has been stressed by many workers. A number of factors, separately or in concert, may be responsible, chief amongst them being prematurity, which deprives

the infant of antenatal storage of iron, cows'-milk feeding, milk feeding for too long a period, twin pregnancy, and chronic ill-health. In each case pallor is the cardinal symptom and the blood picture is that of a microcytic and hypochromic anaemia. Iron is the specific remedy and may be given either as iron and ammonium citrate 2 to 5 grains t d s, according to age, or, if this produces diarrhoea as reduced iron $\frac{1}{2}$ to 1 grain t d s as a powder with sugar placed upon the infant's tongue. The mother should be warned that her infant may pass black stools during treatment. Failure to improve is unlikely and can often be met successfully by raising the dose, continued failure indicates either the presence of a coexistent infection or that the diagnosis is wrong. Occasionally an infant requires a small dose of copper (copper sulphate $\frac{1}{250}$ grain with each dose of iron) before cure is obtained, this is probably not so in more than about 4 per cent of cases. For infants who are weaned and still on milk feeds a dried milk containing iron, such as ferrolac, will save the trouble of dispensing a separate iron preparation. Many authorities urge the prevention of nutritional anaemia by giving small doses of iron as a prophylactic from the age of three months until weaning has been achieved.

In the child iron deficiency from dietetic causes is uncommon, but it may appear as a complicating factor in chronic diarrhoea, such as is seen in coeliac disease, and as the outcome of prolonged infections, of which rheumatism and nephritis are perhaps the most common. Such cases may respond poorly during the active phase of the disease, but as quiescence is established the effect of iron therapy will show itself more fully. A dose of iron and ammonium citrate 10 to 15 grains t d s is adequate.

Hypochromic anaemia—In adults, iron deficiency occurs in a great number of ways, and it is again important to lay stress on the frequency of a characteristic blood count with a low colour-index as the criterion in diagnosis. When no causative factor, such as prolonged oozing of blood from a chronic gastric or duodenal ulcer, can be found, it is usual to describe the condition as idiopathic microcytic or hypochromic anaemia. This condition is much more common in women than in men and

is usually accompanied by achlorhydria (a rather unnecessary point as far as routine diagnosis is concerned), spoon shaped finger nails and a glazed tongue, and sometimes by a palpable spleen, dysphagia is sometimes present. The triad of anaemia, glossitis and dysphagia is described as the Plummer-Vinson syndrome, this syndrome may also be seen in macrocytic anaemia, and it is as well to remember that not a few cases of dysphagia with anaemia that respond to iron, even with apparent improvement of the dysphagia, have a carcinoma of the hypopharynx or oesophagus. Treatment of idiopathic microcytic hypochromic anaemia requires large doses of iron and this may be given in many ways, for simplicity, either iron and ammonium citrate 40 grains t d s or Blaud's pill 30 grains t d s should be recommended, traces of copper are not of proven use in adults, but if achlorhydria is known to exist dilute hydrochloric acid, 30 minims, should be taken with meals, either in a medicine or in lemonade. This anaemia has a rather strong tendency to relapse, and it is better to give a course of iron therapy every second or third month after the anaemia has disappeared to prevent recurrence. The dose should be half of that used in the initial treatment and it is probable that the patient will need such maintenance of the iron reserves for the remaining period of life. No case of microcytic anaemia should be accepted as idiopathic until all possible contributory causes have been excluded, this is particularly important, because iron therapy will frequently cure the anaemia, leaving some contributory lesion more masked than before. The diseases of importance requiring exclusion are chronic bleeding peptic ulcer, carcinoma of the alimentary tract, bleeding piles, menorrhagia, and frequent epistaxis.

Anaemia is prone to occur in steatorrhœa, when it may be and, in ulcerative colitis, often is, microcytic and hypochromic in type, treatment with iron and ammonium citrate, 30 grains t d s, is of considerable value in these cases.

In pregnancy it is not unusual to observe anaemia, this may be normocytic and due, it is believed, to physiological hydramia, or microcytic and due to iron depletion, a condition frequently seen when several pregnancies have occurred in

quick succession. The rare pernicious anaemia of pregnancy must also be excluded. Iron is not only of value in treating the microcytic anaemia of pregnancy, in which event it should be given in large doses, but is often, some would say always indicated prophylactically, in which case a dose of 15 grains of iron and ammonium citrate or 10 grains of Blaud's pill given twice a day during the final three months will usually be sufficient.

The unsatisfactory state of therapy in splenic anaemia and the failure of splenectomy to justify its value statistically have reverted attention to medical methods of treatment. The effect of iron on the anaemia of this disease has been favourably commented on by many observers and it should always be employed whatever other methods may also be adopted.

It is now necessary to pass from those anaemias in which iron is a specific remedy to a series in which it is of less obvious value. After acute haemorrhage either externally or from a peptic ulcer, there is no doubt that recovery is more rapid when iron is administered in adequate dosage. The anaemia of chronic diseases such as rheumatoid arthritis, renal disease and chronic septic illnesses, often responds to some extent, although rarely to a degree of completeness, when iron is administered. It is of more doubtful value in leukaemia, lymphadenoma, and malignant disease involving the bone marrow. The custom of giving large doses to patients with pernicious anaemia at the beginning of treatment, especially when subacute combined degeneration is present is based on clinical rather than experimental evidence. The author's experience suggests that this is a valuable procedure and one that should be adopted in the absence of scientific proof of its worth. The anaemia of scurvy is uninfluenced by iron but the type associated with myxoedema will as a rule respond slowly to iron provided that an adequate dose of thyroid extract be given, it must be remembered that some of these cases will lose their anaemia when treated with thyroid extract only.

As a tonic for patients who are recovering from illness or operation, or merely for those who are run-down, iron is frequently used, and although scientific proof of its value is lacking

it is the opinion of many clinicians that benefit is derived therefrom

THE PRESCRIPTION OF IRON

Since iron in sufficient dosage is effective in curing certain anaemias by itself, there is no necessity to prescribe complicated formulae and it is enough to decide two points only, the type of iron and the way in which it is to be given. A number of official preparations and many more proprietary ones exist and the suggestions given here are intended only to indicate a few that are satisfactory in use and not to decry the rest. For the cure of iron deficiency anaemias in adults the following may be recommended —Iron and ammonium citrate, the official dose is too small and 40 grains t d s should be used, since mixtures containing it grow moulds rather easily some preservative, such as spirit of chloroform should be incorporated in the mixture. Blaud's pill, 30 grains t d s, is another effective prescription, but the pills should be used fresh as oxidation tends to harden them to a point where they pass through the system unchanged. Ferrous sulphate has the advantage that a much smaller dose will be effective and, when given in tablet form six daily of a grain each will usually produce the requisite effect. Fersolate (Glaxo) tablets each contain about one grain of ferrous iron in this form and six tablets daily may be accepted as a suitable dose.

When an adjuvant or purely tonic effect is needed, half doses of these preparations may be given. The three official iron syrups in full pharmacopoeial doses all make satisfactory tonics.

The dosage for children of any of the above preparations is to be regarded as proportionate for the child's age, and for infants under a year the therapeutic measures to be adopted for curative or preventive purposes have been indicated on page 252.

CHAPTER XX

IODINE AND IODIDES

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CHAPTER XX

IODINE AND IODIDES

IODINE

EXTERNAL—The use of iodine as a local antiseptic is familiar in every household, in the form of tincture, iodine stick, or ointment of various kinds, such use, and also that as a counter-irritant, is too universal to be given more than a mention in passing. Preparations such as hydrarg biniodide for a general antiseptic solution, Coster's paste in ringworm of the scalp, and Mandl's paint (pigmentum iod co.) for sore throats, are also commonly employed in medicine.

Internal—The most important use of iodine is in the therapy of thyroid disease, that of iodides in conditions in the respiratory tract and granulomas particularly gumma.

IODINE AND THE THYROID GLAND

Action—If iodine is administered to a human being or animal whose thyroid gland either pathologically or experimentally, is in a hyperplastic state with or without hypersecretion, the acini of the gland return towards the normal state of storage of colloid. In human Graves' disease in which hypersecretion, i.e. hyperthyroidism or thyrotoxicosis is present, all the symptoms and signs (nervousness, tachycardia, tremor, exophthalmos, raised basal metabolic rate) are diminished by iodine therapy. For some reason, as yet undiscovered, after a period of about two-and-a-half to three weeks, although iodine is continued, the symptoms and signs begin to recur, but do not reach their previous severity. Therefore, if the hyperthyroidism was gross at the start it can relapse to quite a severe state during this "escape from iodine". If the disease was mild at the outset, the patient may scarcely return to a thyrotoxic state at all. In either event, in spite of the

continued iodine therapy, considerable areas of hyperplasia will be found on microscopic section of the thyroid gland. These facts explain and govern the use of iodine in the treatment of exophthalmic goitre and other forms of hyperthyroidism.

GRAVES' DISEASE

Pre-operative—The main use of iodine is in producing a rapid remission of symptoms in order to lessen the risk of thyroidectomy. The preparation used is Lugol's iodine (liquor iodii aquosus) (5 per cent iodine to per cent potassium iodide in water).

Plummer and Boothby of the Mayo Clinic, in the first report of this method, said that 10 minims t d s of Lugol's solution is the usual dose required to control the hyperthyroidism preparatory to operation, it has since been found that 5 minims t d s is adequate, it can be prescribed in full strength to be taken in milk or as a mixture, 5 minims in 60 minims of water. The improvement in the patient's symptoms is usually striking and starts within three days of taking the iodine. Operation is performed when the pulse rate has fallen to the lowest level which can be reached this will be seen by its becoming constant for two to three days at usually 20-40 beats per minute below the initial rate. The average time required for this is ten to fourteen days.

Before X ray treatment—The same preliminary course of iodine may be used before starting X-ray treatment, to minimize the risk of the temporary exacerbation that may occur with the first dose or two of X-rays.

As pure medical treatment—Opinion is gradually hardening that severe Graves' disease is more certainly cured, and the patient more quickly returned to lasting normal activity, by operation preceded by a course of iodine therapy than in any other way. Nevertheless Graves' disease is self-limiting, and certainly medical treatment—that is, rest in bed, sedatives and Lugol's iodine—has a definite place in its treatment—the indications are—

- (1) In mild cases, when there is an obvious physical or

psychological irritant factor which can be removed in such cases the mutilation of operation is not immediately necessary and can be held in reserve if medical treatment fails. A three weeks' course of Lugol's iodine 5 minims t d s followed, if necessary, by another after six weeks' interval is a good method of treatment.

(2) In mild hyperthyroidism associated with a puberty goitre this will almost certainly get better of itself and the patient can be tided over the period of illness by iodine therapy in such cases Lugol's iodine 5 minims t d s is continued for a month or two.

(3) In post-operative hyperthyroidism (i) most cases have a greater or less degree of exacerbation of their disease after operation the pre-operative course of Lugol's iodine should be carried on for three to four days after operation, (ii) in some cases the symptoms and signs are not completely relieved by operation, however complete the thyroidectomy has been Lugol's iodine, as a continued treatment for a long time, will help to control the hyperthyroidism, X-ray therapy will also probably be advised in such cases.

In these three conditions presumably the escape from the action of iodine occurs just as it does in severe cases but, relapse being always to a lower level than before treatment, such cases may scarcely reach a condition of hyperthyroidism at all.

Failure of iodine therapy—It must be mentioned here that if, as is rarely the case, thyrotoxic patients do not improve on Lugol's iodine 5 minims t d s they do not seem to react any better to increasing the dose, say to 15 minims t d s. Severe thyrotoxic crises, especially if they occur during iodine treatment, do not seem to react to iodine, even in high doses given intravenously this treatment, however, is the only possible one and must be tried. A patient with hyperthyroidism may have been having a course of iodine as medical treatment and, owing to the failure of this, thyroidectomy is advised in such a case it is necessary to stop iodine treatment for at least six weeks before starting the pre-operative course. Only in this

way can another good remission be obtained preparatory to surgery

In diagnosis—On clinical grounds and even after estimation of the basal metabolic rate doubt may exist whether the patient has hyperthyroidism or simply an anxiety state this is a common diagnostic problem. Unfortunately it is not possible to settle the diagnosis by finding out whether or not the patient's symptoms and signs improve with iodine treatment a therapeutic test does not provide a definite answer.

Dangers of iodine in thyrotoxicosis—It is frequently stated that it is dangerous to give iodine to a patient with a nodular goitre and secondary hyperthyroidism owing to the risk of producing a hyperthyroid crisis or auricular fibrillation. In my opinion never having seen this happen in a personal experience of more than eighty cases of this type the risk must be slight the treatment and the untoward events in such cases may be merely coincident.

ENDEMIC GOITRE

The use of iodine in preventing endemic goitre for example in Switzerland and the Great Lake districts of the U.S.A. is an interesting application of science to public health. Although even now it is not clearly understood how iodine lack occurs in areas of the world where parenchymatous goitre is endemic at any rate the incidence of the condition is reduced by making the population take extra iodine to attain this end iodine is added to the ordinary table salt in such amounts that the average person gets 5-10 milligrammes of iodine per day in their normal consumption of salt. Not only is iodine preventive when given to children but it is to a certain extent

curative in patients who have developed the goitre. As has been known since the Phoenicians on the shores of the Mediterranean ate seaweed as a cure for goitre iodine may diminish the size of parenchymatous non toxic goitres it will not cure them.

SIMPLE ADENOMA

As simple adenomas are in reality areas of hyperplasia of thyroid tissue it would seem theoretically correct to give iodine

as treatment. The involution of hyperplastic thyroid does not necessarily result in much reduction in size. Iodine, however, is often given as a medical treatment for a small single simple adenoma.

IODIDES

The usual salt used is potassium iodide, ammonium and sodium iodides are no more effective and are more expensive.

IN RESPIRATORY TRACT CONDITIONS

Action—Potassium iodide is secreted by mucous glands particularly those of the respiratory mucosa. Its action is to cause the secretion of an increased amount of mucus which is thinner and less viscous than normal. Potassium iodide is secreted by the salivary and lachrymal glands and by the intestinal mucosa. This is especially noticeable in iodism and hypersensitivity to iodides.

Indications—(1) Potassium iodide is therefore most useful in any case in which the secretion in the trachea or lungs is so thick and viscous that it causes distress to the patient in the effort to cough it up. This occurs in asthma, bronchitis acute or chronic, the early stages of both lobar and broncho-pneumonia, and post-operative lung conditions. In such cases a useful preparation will be—

R.	Potassium iodide	-	-	-	-	-	10 grains
	Tinct stramonii	-	-	-	-	-	10 minims
	Syr limonis	-	-	-	-	-	60 minims
	Aquam chlorof ad	-	-	-	-	-	½ ounce

(2) It may also be used for stimulating the patient to cough up sputum when the latter is required for testing say for tubercle bacilli. A strong expectorant mixture is—

R.	Potassium iodide	-	-	-	-	-	3 grains
	Potassium bicarbonate	-	-	-	-	-	10 grains
	Ammonium carbonate	-	-	-	-	-	3 grains
	Aquam chlorof ad	-	-	-	-	-	1 ounce

(3) It can be used with advantage to soothe the tracheitis and sore stage of an ordinary cold. The symptoms are much relieved by small doses, 5 grains in a mixture.

FOR GRANULOMAS

(1) *Gumma, gummatus meningitis*—Its action is but imperfectly known. It does not act as a spirocheticide but may possibly have some specific affinity for the fatty acids which form a large part of the chemical structure of gummas. The action of potassium iodide in promoting the absorption of a gumma is so specific and so rapid that it is sometimes used diagnostically. The usual starting dose is 15 grains t d s in a simple mixture which may be increased up to 60 grains t d s, it can also be used in the form of Donovan's solution, liquor arseni et hydrargyri iodidi.

(2) *Actinomycosis*—It is generally agreed that potassium iodide is of great value in the treatment of actinomycosis, especially in combination with X-ray therapy. In these cases it must be pushed to the limit, i.e. until the patient develops mild iodism* and kept at that dosage for three weeks.

MISCELLANEOUS

Iodine and potassium iodide are also sometimes used in the therapy of various other diseases, for example, rheumatoid arthritis. The results are purely empirical the action is inconstant and not at all understood.

DIAGNOSIS

The radio-opacity of many organic and inorganic compounds is used in the X-ray diagnosis of disease. Various preparations are particularly excreted by certain organs, and are used to outline them on an X-ray photograph. Per abrodil and uro-selectan B are the modern compounds mainly used for intravenous injection to give excretion pyelograms of the kidneys. Thirteen per cent sodium iodide is used for retrograde pyelography. Tetraiodophenolphthalein is given by the mouth to obtain an excretion and concentration picture of the gall bladder. Various forms of iodized poppy-seed oil (oleum iodis).

* The symptoms are coryza running at the eyes, salivation with a metallic taste in the mouth and in very sensitive subjects, there may be tachycardia, malaise, and erythematous skin rashes.

atum B.P. addendum, lipiodol, neohydriol) are used by direct intratracheal injection to show up bronchi and bronchioles and also cavities in the lungs; such oils can be injected directly into open sinuses and empyema cavities to show their extent. Iodized oil can be given by suboccipital injection into the cisterna magna to define the level of a spinal block, or by lumbar intrathecal injection in the diagnosis of sciatica due to a protruding intervertebral disc.

CHAPTER XXI

MERCURY

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CHAPTER XXI

MERCURY

MERCURY has a long and honourable therapeutic history. It was used in Greece twenty five hundred years ago, and was known even earlier in Indian and Chinese medicine. Its introduction for the treatment of syphilis is often attributed to Cumanus and Paracelsus, during the great outbreak at the end of the fifteenth century, but inunctions were practised by Arabian physicians five hundred years before this. In the past twenty years it has been largely displaced in such treatment by bismuth preparations, but is still of some importance, although almost dismissed by some recent writers as of historical interest only in the treatment of this disease.

The preparations of mercury and its salts are numerous; some twenty five are given the hallmark of recognition by the British Pharmacopœia and there are a great many proprietary and other preparations. The pharmacologist divides them into five types according to their solubility and degree of ionization, but such a classification scarcely corresponds with the medicinal uses made of the compounds. From the point of view of therapeutics, their actions may be considered as (a) antiseptic, (b) antisyphilitic, (c) purgative, (d) diuretic. Since mercurial poisoning is not unknown even in the course of therapeutic administration, some mention must also be made of this.

MERCURY AS AN ANTISEPTIC

Mercury is pre-eminent among the heavy metals for this purpose. By the choice of suitable preparations and concentrations actions varying between mild bacteriostasis and intense corrosion can be obtained. The action is not as rapid as it is often supposed to be. The mercury is first adsorbed to the organism, and then enters and destroys it. Usually the dis-

infectant action is superficial and is reduced in the presence of blood or other tissue fluids. *Perchloride* (or *oxycyanide*, which is less highly ionized and therefore less irritant but also less active) is commonly used in 0.1 per cent solution for non-metallic disinfection. Metals are attacked and destroyed by such solutions. Some surgeons find it good for their hands, although it does not penetrate the gland ducts as spirit does, it may be less detrimental to the skin. For occasional application to unbroken skin, it may be used dissolved in spirit. There is a wise convention according to which perchloride solutions are tinted blue or pink for easy differentiation from other surgical lotions. Much weaker solutions—0.01 to 0.05 per cent—are used occasionally for wounds and mucous surfaces, but are of limited value because of their poor penetration and rapid inactivation. The non-ionized preparations are also non-irritant but only feebly antiseptic, indeed they are probably only antiseptic at all in so far as they are reduced to ionized forms in the tissues. The fluoresceins yield examples of the class, and *mercurochrome* (sometimes called *mercurochrome-220*) is the best known example. A 1 per cent solution of this dye is used as a penetrating application for mucous membranes, especially of the bladder. Such use is limited by its incompatibility with acids, local anaesthetics, and most alkaloids. The stains can be removed by hypochlorites, or by permanganate followed by oxalic acid. Reference to its systemic action will be made later.

OINTMENTS—For the relief of itching and mild counter irritation of the skin use may be made of black wash (*Lot. hydrarg. nigr.*) or the dilute ointment of the nitrate (*Ung. hydrarg. nit. dil.*) or *calomel* may be used as a dusting powder, especially for syphilitic sores. The numerous ointments are used for various infections and infestations. Thus white precipitate (*Ung. hydrarg. ammon.*) may be used at B.P. strength or weaker for bacterial infections of the skin, ringworm or pediculosis. Blue ointment (*Ung. hydrarg.*) is used as an ununction for syphilis or for the reduction of chronic inflammations in joints or glands, although for this the weaker Scott's dressing

(*Ung hydrarg co*) is usually preferred. For the eye the pharmacopœia provides *Oculent hydrarg oxid* (1 per cent yellow oxide)—a preparation best further diluted in many cases. A favourite ointment for various skin conditions consists of a mixture of equal parts of *Ung hydrarg nit dil*, *Ung zinc oxid*, and *Ung plumbi subacet* (B P 1914). The proportions of mercury may be varied according to the desire for a more stimulating or a more sedative preparation.

MERCURY IN SYPHILIS

With the introduction of the organic arsenicals in 1909, it was thought that the use of mercury in syphilis might become superfluous. But mercury re-established itself for use in the rest periods between courses of arsphenamine and for its value against arsenic resistant organisms. With the spread of the use of bismuth since 1921, mercury has diminished in importance. Bismuth proved less liable to provoke toxic sequelæ, and more potent against the spirochæte, or at any rate quicker in action. Relapses, however, are claimed to be more frequent after bismuth than after mercury treatment.

MODE OF ADMINISTRATION—In the early days of this century mercury was generally given by mouth—as the perchloride to adults and as grey powder to children—and repeated small doses were given, often with a little opium, to minimize intestinal disturbance. An alternative route was to give blue ointment by *inunction* 60 grains daily, choosing fresh and non-hairy skin areas. Such inunctions are time-consuming, laborious, and rather messy, and make secrecy in treatment well nigh impossible. But the persistence of the method in spite of all its difficulties indicates its reliability.

With the advent of the arsenicals, and the growth of the venereal disease clinic, treatment by *injection* replaced the oral course. Injections made more certain that the treatment was not overlooked, and made the dosage more precise. A 10 per cent suspension of mercury or mercury salicylate, or a 5 per cent suspension of calomel is injected in weekly or bi-weekly doses of 8 to 15 minims. Such injections are not devoid

of pain and discomfort, but this can be reduced by using, as a suspending agent, wool fat 50 parts, olive oil 23 parts, camphor and creosote of each 10 parts. The absorption from the intramuscular depots is rather irregular. About three fourths of the mercury is eventually excreted by the kidneys and may damage these organs. With intramuscular bismuth there is less pain from the injections, less irregularity in absorption, and a swifter action on the spirochaete.

Mercury tends to be used only for patients who refuse injections but who will take *oral treatment*, or who are intolerant of arsenicals or bismuth. Certain preparations of bismuth which are suitable for oral administration in syphilis have recently become available, so the use of mercury may become still less common. The most common form in which to give the drug is probably Hutchinson's pill—a grain of grey powder and a grain of Dover's powder twice or thrice daily, according to tolerance. An alternative pill contains $\frac{1}{8}$ grain of perchloride. For syphilitic ulceration in the mouth a solution of 0.05 per cent perchloride in dilute acidulated glycerin has proved useful. In syphilitic lepers avenyl—a solution of mercury in hydnocarpus oil—has given promising results.

OTHER INFECTIONS

Like most antiseptics, mercurials have been tried in the pre-prontosil period in the treatment of many streptococcal and staphylococcal infections. Mercurochrome has been given in doses of 20 c.c.m. of 1 per cent solution, intravenously, in plague and undulant fever. It is admitted that the reactions may be severe. It could hardly be a real specific, and is probably an example of "auto immunization"—a shock therapy for which doses up to 5 mgm. per kgm. intravenously have been recommended. The margin of safety is scarcely adequate to justify such measures. Mercurochrome is not spirochaeticidal in such doses in man.

PURGATIVE ACTION

Since mercury, however administered, is in part excreted by the gut, some irritant action and resultant diarrhoea are

common during its administration. In practice the tasteless and insoluble preparations, calomel (*hydrarg subchlor* $\frac{1}{2}$ to 3 grains) and grey powder (*hydrarg cum cret* 1 to 5 grains) are used to stimulate peristalsis. They are as a rule without action on the stomach, but in the intestine they are probably transformed in part into the irritant perchloride or other soluble form, and these increase intestinal movement reflexly throughout the length of the gut. They are slow acting and should be given at night and followed by a saline in the morning to reduce the risk of both absorption and diarrhoea. Tolerance to their action on the gut is developed, hence they should not be used in chronic constipation. They are usually non gripping but both nausea and gripping are sometimes produced, especially by calomel. A bacteriostatic action on the intestinal flora and some chalagogic effect are claimed by certain writers, but have scarcely been established. A recent suggestion that calomel purges because it is converted into metallic mercury in the intestines is pharmacologically untenable. It is obviously dangerous to give a mercurial purge if it is to be held up in the intestine and absorbed. This danger is increased by repeated administration. During the administration of iodides, mercurials should be avoided unless absorption is desired, as in the treatment of syphilis.

The administration of $\frac{1}{2}$ to 1 grain of grey powder to young children during teething troubles may originate in the marked increase in salivary secretion which is seen in mercurialism. Probably any benefit which such treatment confers is secondary to the stimulation of, and other possible actions on, the bowel.

DIURETIC ACTION

In the course of the use of mercurial purges an increase of urinary excretion was sometimes observed—most marked when the mercury failed to purge or was not completely swept from the alimentary tract by a following saline. This diuretic effect is more marked when the tissues are oedematous and especially when the dropsy is cardiac in origin. But the diuresis produced by calomel or grey powder, even in repeated doses, is insignifi-

cant in comparison with that which follows suitable treatment with various organic mercurials. The first of these to be widely used was *novasurol*, but this was given up after the discovery of such more potent and less toxic drugs as *neptal*, *novurit* and *salyrgan*. This last drug is included in the 1936 addendum to the British Pharmacopœia under the name of mersalyl, and an official injection is provided also which contains 10 per cent of the salt in water, containing 5 per cent theophylline and a little alkali.

The recommended dosage is 8 to 30 minims, by intramuscular or intravenous injection. It is customary to begin with a deep intramuscular injection of 8 minims and to give 15 minims the next day and if necessary 30 minims on the fourth day, repeating this dose every second day if necessary. The injection should be given in the early morning, so that the peak of the diuresis is well past before sleeping time and it is well to avoid œdematosus areas as sites for injection, as cellulitis may develop in such.

The diuresis begins in an hour or so, increases steadily to a maximum in eight or twelve hours and may persist for thirty-six hours, and amount to twice or thrice the normal excretion. The usual explanation of the mechanism of the diuresis is that the drug inhibits normal tubular reabsorption without irritation. It has also been suggested that the drugs act by opposing the normal anti diuretic effect of posterior pituitary principles on the kidney. It is important to remember that this group fails when there is nitrogen retention and is definitely contraindicated in arteriosclerotic nephritis.

If the response to intramuscular medication is unsatisfactory the drug may be given intravenously. Its action may be enhanced by digitalization and also by making the urine acid. For this latter purpose ammonium chloride in 15 to 20 grain doses q.i.d. may be given for two or more days and probably best in cachet form. The least disturbing method of administration of the mercurial is to give it as a suppository. Such are available for all three of the proprietary preparations mentioned, containing 0.5 gm of drug in each. Any rectal disease—even a haemorrhoid—is a contraindication to such

administration. If symptoms of rectal irritation arise, treatment by this route should be discontinued at once.

In cardiovascular syphilis with a failing heart part of the favourable reaction to organic mercurials has been attributed to a spirochaeticidal action. Although these drugs are effective against this organism in certain experimental animals, the balance of the evidence is against any significant action of this kind in man. Good results have been claimed in arthritis, bronchorrhœa, hepatic cirrhosis, eclampsia uncomplicated by pyelonephritis and nitrogen retention, Ménière's syndrome, and in certain cases of obesity.

MERCURIAL POISONING

The usual three types—acute, subacute and chronic—are described. Certain features are common to all cases of mercurial poisoning.

Acute poisoning usually results from the careless or too generous use of the perchloride, and the mucous membrane which has been exposed to the action of the drug suffers from irritation and corrosion. When large amounts are absorbed, the patient may die in a few hours from circulatory collapse. I remember an example of this in a woman who had inserted a tablet of perchloride, meant for the preparation of a douche, into her vagina. In less acute cases, stomatitis is developed in about a day, with complaints of a harsh metallic taste, excessive salivation, and burning and swelling, which may spread to the glottis. By the second day, owing to irritation of the alimentary tract, there is nausea and vomiting, with diarrhoea and violent tenesmus. The kidneys too have suffered, since they also are concerned in the excretion of mercury, and the urine may contain albumin and casts, or may even be completely suppressed. The patient becomes collapsed, with an irregular thready pulse, rapid respiration, a cold clammy skin, pinched features and sunken eyes. Death usually results in about a week. If the patient vomits almost at once after swallowing the mercurial, his chances of recovery are fair. Otherwise the drug is rapidly fixed to the tissues, and antidotes and emetics are of little value as they only eliminate it in traces. Sodium

formaldehyde sulphoxylate is the most recent precipitant to be introduced. This is used for lavage, and has also been given by slow intravenous injection in doses of 100 c.c.m. of 10 per cent solution.

Subacute poisoning may arise, but should never reach a serious stage, when mercury is used for syphilis. Stomatitis, colitis, and an interstitial nephritis may also occur. More rarely, especially after inunctions, there is a mercurial dermatitis. Almkvist teaches that the stomatitis starts in the gingival pockets, and is due to a precipitation of mercury sulphide in the capillary endothelium by the interaction of ionized mercury and infected tissues. If the warning afforded by the salivation and soreness of the gums is not taken, the condition may go on to a loosening of the teeth, a blackening of the edges of the gums, and swelling and ulceration of the tongue. In the more chronic form there may be necrosis of the jaw. The colitis may be explained on similar lines. The salivation is difficult to explain—it is not due to the concentration of mercury in the secretions but degenerative changes in the parotids have been described. Stomatitis does not arise in infants, nor in the edentulous and dental attention and the regular use of a peroxide mouth wash help to prevent it.

Chronic poisoning (mercurialism or ethism) occurs in workers who are handling mercurial solutions or breathing its fumes. At one time about half such workers suffered. Improved conditions have reduced this incidence to about 2 per cent, and nowadays, as a rule, only mild poisoning is seen. In these cases the kidneys are often little affected—they can eliminate the lower concentrations of mercury for a long time without danger. Many miscarriages have been attributed to working with mercury. The usual stomatitis has added to it nervous and nutritional disturbances. Tremors (hatter's shakes) are notoriously common in felt workers who use mercury nitrate solutions. It is stated that they never occur in total abstainers from alcohol. True ethism, as seen in thermometer and barometer makers, is marked by a curious irritability and restlessness, and often by shyness. Treatment consists in removal of affected workers from all contact with the metal and persuading them

to give up alcohol until they are better. Prophylaxis is more important than treatment, and enlightened legislation has done much to protect the workers.

The reader who seeks further information on mercury will find a full general account with many references to original authorities in T Sollmann's "Manual of Pharmacology", published by Saunders—5th edition, 1938. The therapeutic uses are all considered in the recent "Textbook of Medical Treatment" edited by Dunlop, Davidson and McNee (Livingstone, 1939). There are many good accounts of mercurial poisoning. Hamilton's "Industrial Toxicology" (Harper, 1934), Leschke's "Clinical Toxicology", which contains fascinating case histories (Churchill) and D Hunter's "Occupational Diseases" (London Hospital Gazette, 1935). The industrial practitioner and medical sociologist will find much to interest them on their specialities in the International Labour Office's "Occupation and Health" (Geneva, 1935).

CHAPTER XXII

QUININE AND ALLIED DRUGS IN THE TREATMENT OF MALARIA

QUININE, derived from cinchona bark, has been regarded for many years as the specific remedy for malaria, one of the most widespread of tropical diseases. Efforts to find a substance possessing properties lacking in quinine have resulted in the evolution of other preparations of value but the ideal drug has yet to be evolved. Taken by the mouth quinine is normally rapidly absorbed from the duodenum and small intestine. In the duodenum the alkaline salts precipitate the quinine alkaloid which, after absorption, circulates in the blood as a quinine base. The time of circulation is short, some of the drug being deposited in the liver, spleen, and other tissues, the remainder being excreted in the urine in which its presence can be shown by the Tanret-Mayer reagent, usually about half an hour after ingestion. How quinine acts on the malarial parasite is not yet clear. Evidence favours both direct and indirect action, direct through a disintegrating action on the parasites while in the blood stream, indirectly by activating the body defences by means of the cells of the reticulo-endothelial system. The drug has no action on the sporozoites injected by the infecting mosquito. In daily doses of 15 to 20 grains it causes disappearance of the trophozoites of all types of malaria from the blood stream in five to seven days. It also affects the pre gametocytes and gametocytes of all types, but its action on the gametocytes of *subtertian* malaria is only very slight. Its action appears to be greatest at the time of sporulation in the human cycle.

ADMINISTRATION OF QUININE

Quinine in solution by the mouth is best. When the bitter taste is troublesome, cachets, tablets or pills can be used.

Sugar coating may prevent absorption of the tablet, so in the tropics it is wise to test how the tablet will dissolve by placing it in a tumbler full of water. For children euquinine (ethyl carbonate of quinine, dose $1\frac{1}{2}$ to 15 grains) or lacquin (ethyl carbonate of quinine, $2\frac{1}{2}$ grains to 60 grains of dried milk) are useful in overcoming the taste trouble. The sulphate, hydrochloride and dihydrochloride are the forms of the drug commonly used. Their solubility, and hence their suitability for intramuscular injection, increases in the order named. Large doses of 50 grains daily are not more effective than the usual doses of 20 to 30 grains daily and lead more rapidly to cinchonism. Children bear quinine well, about $1/20$ th of the adult dose is advised for each year of life up to fifteen years of age.

A routine method is to give 10 grains, t.i.d. for several days until the temperature reaches the normal, then 10 grains twice daily for ten days, and then 5 grains twice daily with iron and arsenic in mixture or tablet form for two months. In the short course the appropriate dose is given t.i.d. until the temperature remains steady at the normal, and then for four days twice daily. This is recommended by those who consider the long course deleterious to the patient's general health, but relapses follow more frequently and demand repetition of the course.

To counteract the *acidosis* and *hypoglycaemia* which occur with a malarial attack, Sinton's method of combining quinine with an alkaline mixture, glucose being administered at the same time, gives good results.

In *pregnancy* quinine should not be withheld. Acute malarial attacks, unless quickly and properly treated, will most likely lead to abortion. Half the usual doses should be given, but twice as often. When there is a history of malaria 5 grains daily should be given in the puerperium. Quinine is secreted in the breast milk. Labour, operations and all factors causing shock or physical strain, may light up the disease in patients who have previously had malaria and it should be remembered that malaria can be transmitted via the placenta.

When *blackwater fever* is feared quinine should never be given in large doses, but in repeated small doses of $2\frac{1}{2}$ grains or less. The drug causes contraction of the spleen and in patients

infected with certain strains of subtertian parasites this contraction may cause destruction of some of the erythrocytes and also possibly set free haemolytic substances into the blood stream, sufficient to ensure the onset of the blackwater fever. Such patients should be given plenty of alkaline fluids by the mouth or intravenously with all precautions, suppression of urine is less likely when its reaction can be maintained on the alkaline side. Glucose by the mouth or intravenously in sterile 5 per cent solution is also indicated as it has been shown to prevent the haemolysis of the erythrocytes by quinine.

One rule must never be forgotten—no delay can be allowed in giving quinine to patients with malignant or subtertian malaria or with severe symptoms.

In *cerebral malaria* inhalation of amyl nitrite may help to prevent accumulation of parasites in the brain and render them more accessible to the quinine. Injection of 5 to 10 minims of adrenaline solution 1/1000 intravenously may also aid the accessibility. When coma or convulsions have supervened lumbar puncture and withdrawal of 20 c cm of fluid by reducing cerebral anaemia, may assist the action of the drug when little benefit follows intravenous injection.

INTRAMUSCULAR ROUTE—*Indications*—Severe and urgent symptoms, such as coma, convulsions, hyperpyrexia, delirium, nausea, vomiting and diarrhoea preventing absorption, or in patients who cannot be trusted to swallow the drug. The dihydrochloride is the best salt, in 5 to 10 grain doses. Ampoules (9 grains to 2 c cm saline) are obtainable. The buttock (never the arm) in its upper and outer quadrant is the best site. Absolute asepsis is necessary.

Disadvantages—Pain and necrosis of muscle are caused, sloughing nerve injury, and tetanus have followed. Abscess may arise when the patient has already a septic focus elsewhere, such as tonsillitis, septic teeth, or prostatitis.

INTRAVENOUS ROUTE—*Indications*—(1) When rapid action of the drug is needed as in cerebral algid, and pernicious subtertian infections, with severe symptoms as detailed above, (2) when very numerous parasites are found in the blood slide.

As mentioned on page 283, the use of adrenaline or lumbar puncture may assist its action

Of the dihydrochloride, 5 to 10 grains in 10 to 20 ccm of sterile water or saline are given, and slowly, as a fall of blood pressure is caused. Concentrated solutions may cause collapse and syncope and, as toxins liberated from the destroyed corpuscles by the circulating quinine are also a cause of cardiac failure, it is advisable to follow the intravenous quinine with 5 to 8 minims of adrenaline 1/1000 solution by the same route, or it can be added to the quinine injection. If necessary the quinine injection can be repeated in eight hours.

Advantages of route—No loss of absorption and rapid action of drug.

Disadvantages—Rapid fall of blood pressure with possibly serious sequelæ. In patients with quinine intolerance death may ensue, phlebitis and thrombosis have occurred.

CINCHONISM—Symptoms which follow large doses are headache, ringing in the ears, giddiness, nausea and deafness. Patients sensitive to quinine may show vomiting, photophobia, dyspnoea, dysphagia, itching, cutaneous eruptions and haemorrhages, bleeding from mucous membranes, pyrexia, haemoglobinuric fever, prostration, tremors, palpitations, local oedema, cachexia, collapse, syncope, or amaurosis after excessive or prolonged use of moderate doses.

Prophylaxis—The usual practice is to give 5 to 6 grains daily when in a malarious region, but 15 grains twice weekly or for two days at the week-end is effective with some subjects.

PLASMOQUINE PRÆQUINE

In testing various compounds derived from methylene blue plasmoquine was discovered. It is N-diethyl amino-iso-pentyl-8-amino-6-methoxyquinoline. It is now being made in Britain under the name of præquine (May and Baker, Ltd.). Pamaquin is its recommended British Pharmacopoeial title. This drug destroys all forms of benign and quartan parasites but only the crescentic forms of subtertian malaria and this latter property gave great hope of usefulness in anti malarial work.

Its ability to prevent the crescents developing in the mosquito can check malarial spread, but unfortunately the prophylactic dose is too near the toxic one to allow its use as widely as, and with the safety of, quinine, and the possibility of inducing black-water fever must always be remembered.

PLASMOQUINE was supplied in 0.02 gm tablets and the course was one tablet three times daily after food for five or seven days and then, after a four day interval, one tablet three times daily for three days in each week for four weeks.

Toxic symptoms are cyanosis, headache, abdominal pain, nausea, vomiting, renal pain with methaemoglobinæmia and methaemoglobinuria, haemorrhagic nephritis, and toxic necrosis of the liver. It is contraindicated when blackwater fever is feared, the methaemoglobinuria caused by the drug may lead to a mistaken diagnosis of that disease. Owing to its toxicity, parenteral injections are not recommended.

A standard course of 0.04 gm plasmoquine and 20 grains of quinine daily for twenty-one days has been used in groups of patients abroad. Toxic symptoms arose usually between the sixth and ninth day, but on discontinuing the plasmoquine for three or four days this risk subsided and the patients were able to resume the drug and complete the course. The combination of quinine with plasmoquine markedly reduces the relapse rate of all the malarias.

Prophylactically a dosage of three tablets daily for five days in each month is stated to give good results free from toxic symptoms.

PRÆQUINE is supplied in 0.01 gm tablets. The usual course is one tablet three times daily for five days. Following a course of quinacrine (atebrin), and after an interval of two or more days, it can be given for five days with the aim of eliminating crescents. Caution in its use is advised when patients have severe anaemia or hepatic dysfunction.

PLASMOQUINE COMPOUND AND QUINOPLASMINE

Plasmoquine combined with quinine acts more effectively and its toxic effects are less frequent and intense, duration of

treatment is shortened, and *quinoplasmine* is stated to reduce the relapse rate of benign quartan and, in some patients, of subtertian malaria better than any other method. It should be remembered, however, that the relapse rate varies with the strain of the parasite.

Quinoplasmine tablets contain 0.01 gm plasmoquine with 0.3 gm quinine. One tablet t.i.d. for six or seven days, or courses of four to five six-day treatments at four-day intervals, can be given.

Plasmoquine tablets contain 0.01 gm plasmoquine with 0.125 gm quinine. The course for an adult is the same as for *quinoplasmine*, using two tablets t.i.d. p.c. For children up to four years, one tablet daily; four to six years, one tablet twice daily, and one tablet three times daily for six to ten years, is given. They can also be given in pregnancy and the puerperium. Combined, the drugs are effective in all forms of malaria, but blackwater fever may occur.

ATEBRIN, QUINACRINE AND MEPACRINE

Atebrin (acriquine, Russian), like plasmoquine evolved by German effort, is dihydrochloride of 2-methoxy-6-chloro-9-(4-diethylamino-1-methylbutyl) aminoacridine. In malaria as a rule it does not bring the temperature down as rapidly as quinine, the average being three days to one and a half to two days with quinine. It often gives a sense of well being, is well borne in pregnancy, and is indicated when an idiosyncrasy to quinine exists. Relapse is less frequent than with quinine in benign and certain strains of subtertian infections. It appears to be the safest drug when blackwater fever is feared, but a few cases have been reported following its use.

Atebrin acts on all forms of malaria. A daily dose of 0.3 gm eliminates the trophozoites of benign and quartan from the peripheral blood in three days and those of subtertian in four days in 90 per cent of patients. On the pre-gametocytes of benign and the gametocytes of benign and quartan its effects are slightly more marked than those of quinine. It acts on the pre-gametocytes of subtertian malaria, but only slightly on the

gametocytes It does not prevent, as plasmoquine does, the exflagellation of the crescentic forms

The adult dose is one tablet (0.1 gm) three times daily immediately after food for five to seven days, repeating this after a week's interval Children take atebrin well, up to one year $\frac{1}{2}$ tablet, to four years 1 tablet, to eight years 2 tablets, and after eight years 3 tablets, are given daily

Milder *toxic effects* noted are epigastric pain, headache and, in children, vomiting and diarrhoea Being a dye substance, yellowish pigmentation of the skin often occurs, this may take some weeks to disappear but, as some recently made preparations of atebrin are coated pigmentation is now less frequent Exposure to direct sunlight is better avoided for three or four weeks after treatment The pigmentation may simulate jaundice, but as a rule it does not appear until the third day of treatment, it may not involve the sclera and its intensity varies with the regularity of bowel movements Undue excitement, mild or transient psychoses, and even more serious mental symptoms have been recorded, but are more frequent when the drug has been given by injection Cumulative in action and excreted slowly, the intervals between courses should be observed to avoid toxic symptoms appearing later The urine becomes a bright yellow Atebrin is contraindicated in the treatment of known alcoholics, as acute jaundice may develop

ATEBRIN MUSONATE is a form of the drug, used for injection intramuscularly in 0.1 to 0.3 gm doses, or 0.1 gm intravenously, dissolved in 3 to 9 c cm of sterile water The solution should not be heated nor stored for any length of time Intravenous injection, indicated in heavy infections and when complications are severe, should be given slowly, as the margin of safety is not wide In severe subtertian and cerebral infections quinine by injection is preferable and much more reliable (Manson Bahrt) Additional *toxic effects* may be gasping quickened respiration circulatory failure and collapse, pyrexia, anorexia and wasting Intramuscular abscesses have followed injections

The combined administration of atebrin and plasmoquine is

dangerous, it appears to aggravate the toxicity of each; but a course of atebrin for five to seven days followed by plasmoquine for three to five days has given favourable results with the relapse rate satisfactorily reduced, and this sequence of one upon the other is apparently safe

Prophylaxis—Doses of 0.2 gm given twice weekly to groups of patients abroad, although causing pigmentation, are reported to have given satisfactory results. A daily dose of half a tablet is claimed to have kept students in Africa malaria-free for three and a half years

QUINACRINE AND QUINACRINE SOLUBLE (M & B) AND MEPACRINE (ICI)

These are forms in which British-made atebrin is now supplied. The tablets of quinacrine contain 0.1 gm and with quinacrine soluble, the form for injection, the contents of the ampoule are dissolved in 1.5 to 5 c.c.m. sterile distilled water. Tablet dosage is as for atebrin. Mepacrine dosage is similar. Mepacrine hydrochloride and mepacrine methanesulphonate respectively are the pharmacopœial titles now adopted for these preparations

SULPHONAMIDES

These preparations do not appear to have as effective an action on malaria as the drugs already mentioned. Chopra and his colleagues found prontosil controlled the symptoms and caused parasites to disappear from the peripheral blood following doses of 3 to 4 gm daily for five days. Relapses occurred in fourteen days when only 2 gm daily had been given. The drug destroyed all forms of benign and quartan, but only the asexual forms of subtertian malaria. The crescents were not affected. Using M & B 693 they found it necessary to increase the dose of one tablet (0.5 gm) three times daily to 4 gm daily to prevent relapses in hospital. All forms of benign and the asexual forms of subtertian were destroyed, but crescents were unaffected. Quartan parasites persisted for two days after treatment. In all types symptoms were controlled.

Septasine appears effective against all forms of benign, but only against the asexual forms of subtertian malaria. More recent reports on the action of the sulphonamides are not nearly so satisfactory.

ARSENICALS

These are often given as general tonics and to aid repair of anaemia in malarial patients. Whittingham states that N A B is lethal to parasites and, like adrenaline, by driving the parasites into the blood stream, facilitates the action of quinine. For recurrent attacks 0.45 gm is given in the morning, then quinine 10 grains at night and 10 grains t.i.d. next day. This is repeated at seven or fourteen days interval for six to eight treatments. Salvarsan and neosalvarsan, which are used intravenously in the Sudan and other parts of Africa, are chiefly beneficial by the tonic effects produced. Mepharsen, a trivalent arsenical, in doses of 0.04 to 0.06 gm intravenously, depending on body weight, is claimed to cut short a malarial attack in 90 per cent of patients after a single injection. The injection can be repeated in a week.

Diemenal, a salvarsan derivative, has been given by injection as a cure for malaria, but its effectiveness is still doubtful.

Stovarsol (tablet 4 grains one or two daily for ten days) appears to act better when combined with quinine. Tryparsamide apparently does not affect the parasites.

QUINIDINE

Quinidine and its salts have curative effects similar to quinine on all forms of malaria. They are more depressant to the heart. Some consider them more effective against benign tertian malaria. Quinidine sulphate is given morning and evening in 10-grain doses for two days and then 10 grains at night for three days.

Cinchona febrifuge contains the total alkaloids from the bark. It is cheap, and is effective in benign tertian malaria, 10 grain doses are given twice daily for ten days.

OTHER DRUGS AND PREPARATIONS

Tebetren—A combination of quinine with an acridine dye and a derivative of cholic acid, is rapid in action and is stated to check the formation of gametocytes. It is slightly toxic. The course is two tablets of 4 grains four hourly for thirty doses. It can be given by injection.

Malarcan—Somewhat similar to tebetren, is slower in action and relapse is more common.

Aristochin—This contains 96% per cent quinine and is tasteless. Dose 1 to 10 grains according to age.

Certuna—Dialkylamino-oxyquinolamino-butane possesses action comparable with plasmoquine, but with less toxicity. Dose 0.2 gm daily for six days.

Cilional—This drug is similar to certuna.

Rodoquine (Fourneau 710)—A quinoline derivative claimed to be less toxic than plasmoquine and equally effective.

M3 or manganese iodo-mercurate—Results after treatment are favourable as a prophylactic it is disappointing. The dose is 1 to 8 pills every second day.

Esanofele—A popular remedy containing quinine bisulphate 1/2 grains (0.09 gm), arsenious acid, 1/72 grain (0.0009 gm), citrate of iron 2/5 grain (0.027 gm), powdered herbs 1/4 grain (0.0145 gm). Dose under six years 2 pills, under fourteen 4 pills, adults 6 pills a day. Propylactically 2 pills a day.

Ascoli's treatment—This consists in giving adrenaline intravenously in doses increasing from 1/100 mgm to 1/10 mgm and then repeating the last dose twenty times. Reduction of splenomegaly, decrease of anaemia, improved weight and general health are claimed to follow it, as well as increase of the efficiency of quinine given subsequently.

Methylene blue acts on quartan malaria. The dose by mouth is 1 to 5 grains. It can be given intravenously in 0.05 gm in 5 c cm sterile water. It is useful to patients refractory to

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CHAPTER XXIII

TONICS

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CHAPTER XXIII

TONICS

THE term tonics is falling out of favour with writers on pharmacology. Few textbooks refer to tonics as descriptive of a drug's general action nor are the references very gracious. Hare stated —

tonics are used to increase vital activity. They are indicated in local or general systematic depression and contraindicated in cases of inflammation or excitability with excessive functional activity (see bitters)

Gunn in his edition of Whitla's textbook says —

Tonics are strictly speaking medicines which improve the tone of the part on which they act thus it may be on the stomach as the pure vegetable bitters and all stomachics or on the cord as strychnine or on the heart as digitalis or on the nervous system as quinine and the valerenates or on the circulating fluid as iron. The term tonic is too vague to convey any precise meaning and is best avoided.

Paris writing one hundred years ago gave quite a good description when he stated that tonics are substances whose continued administration gives strength and vigour to the body without producing sudden excitement or subsequent depression. He insisted that they act slowly and progressively not overtaxing the organs stimulated thus avoiding subsequent collapse and gradually producing a general improvement in the functioning of other organs increasing their power and so by an ascending scale restoring general health. He considered them definitely *inadvisable in health*. It is interesting to note that the tonics employed by Paris were very much the same as those used to-day—bitters cinchona and quinine strychnine and iron.

Although pharmacologists have abandoned the term tonics practitioners still use it and patients ask for and insist on

getting tonic medicines What then does the practitioner understand by a tonic? I think the way to put it is this He distinguishes between a curative remedy which arrests or removes a morbid condition and restricts the term tonic mainly to those remedies which, by improving the working of some bodily function, give resulting benefit to the general health He does not use the term tonic in connexion with colchicum in gout, or sodium salicylate in acute rheumatic fever He uses the term tonic purely for an effect which is produced more indirectly, a bitter to promote appetite in convalescence or *nux vomica* for patients complaining of a general feeling of slackness, which Lauder Brunton's patient so well described as ' feeling like a stiff collar after all starch had been taken out of it ' I think there is also in the practitioner's mind the feeling that a tonic is a temporary form of treatment, which should start an improvement, which will gather momentum and go on by itself Give a convalescent a bitter to start his appetite he will take more interest in things, exercise more sleep better and his appetite will come back naturally

THE BITTERS

Among the tonics most frequently used are the bitters They have been employed since the earliest records of medicine They formed a large proportion of the drugs used by Hippocrates The Greeks used them both externally for inflammatory lesions and internally for gastro intestinal disorders Gradually they came to be employed more particularly for medication of the stomach chiefly as appetizers and improvers of digestion When it was realized that the essential factor in their action was their property of pure bitterness the number employed was curtailed, and nowadays the ones used mainly are *gentian*, *quassia strychnine* and *nux vomica*, and *guinine*

MODE OF ACTION—The mode of action of the bitters has been frequently investigated but the findings are confused and contradictory Most of the early work was done on healthy dogs, under conditions which permitted the test drugs to be applied directly to the stomach or allowed to operate on the

mouth only. Perhaps the dog is not a good animal for this purpose. It responds by intense salivation and does not seem to like bitters. Actually sheep might have been more suitable, as it is stated that they pick out bitter plants in pasture. The healthy dog usually gave negative results as regards any definite increase in amount or quality of gastric juice when the bitter alone was applied either to the mouth or stomach. Borisson first investigated the reflex effect of oral administration using a dog with a severed oesophagus, the upper end being brought to the surface. He found that sham feeding with meat caused a greater secretion of gastric juice after oral administration of a bitter. The most frequently quoted investigation is that of Moorhead. In order to test the bitter action in a condition akin to that in which they are used in human therapy, he rendered his dogs cachectic by repeated bleedings. In health, his dogs showed no response to oral administration except salivation, the same dog in a cachectic state responded differently. Bitters, whether applied orally or directly to the stomach, improved the appetite of the dogs, which ate larger quantities of food, although not quite up to that partaken when in health. Stopping the bitters resulted in less food being taken. In the cachectic dogs the administration of bitters orally, but not by direct application to the stomach, caused an increase in the quantity and quality of the gastric juice secreted in the hour following the meal. Pepsin remained constant but both free and combined hydrochloric acid were increased. Moorhead used in these experiments amounts of the bitters which corresponded to those used in human therapy. Carlson's observations on human beings in good health show that the bitters in the mouth inhibit hunger contractions of the stomach, and sense of hunger, but do not increase the amount of early gastric juice. Many experiments were carried out by him on a man, otherwise healthy, who had complete oesophageal obstruction and a permanent gastric fistula.

This man used to chew his food and then insert it into his stomach with a syringe. While the experiments were being carried out the man went about his ordinary work chose his own food had his gastric response tested and now and then was given therapeutic doses of tinctures of gentian, calumba hop condurango and

Easton's syrup Special attention was paid to the appetite secretion of gastric juice i.e. that which occurred within the first twenty minutes The tonics whether given by the mouth or directly applied to the stomach produced no increase in amount of acidity or pepsin content of the appetite juice nor did they render an unpalatable meal more palatable

At Carlson's suggestion Moorhead completed an extensive series of tests with bitter tonics on five hospital patients suffering from chronic cachexia and poor appetite He used again the test of measuring the amount of food consumed to determine whether or not the tonics did actually increase the appetite He found as in his dog series that the amount of food consumed on tonic days was greater than on days when no tonic was given Some increase of consumption occurred if the patient was unaware of the possible action of the tonic From these experiments it had been concluded that in health the bitters are without much effect upon the appetite or secretion of gastric juice but that in diseased conditions they have a beneficial action Some writers go so far as to assert that the action is purely psychological but the general opinion is that the effects are reflex from the stimulation of the taste buds appreciating the bitter taste on the dorsum of the tongue It is also customary to deny that the bitters have any action when applied to the stomach only But amongst the experimental findings are reports of a later effect of the bitters upon the intestine shown by increased intestinal absorption of drugs after the previous application of bitters to the stomach

Recently observations by Ivancevic and Kadruka on healthy men indicate that the direct application of bitters to the stomach either in the form of rice capsules or by duodenal tube produces changes in the contour picture of the rugae of the stomach obtained by X rays Using thin barium meals the upper parts of the rugae are covered with adherent barium whereas the depressions between the rugae are free from barium They found that whereas the oral application of gentian produced no change in the X ray picture the direct application of gentian to the stomach caused the folds to become wider and increase in height and there was evidence of increased secretion of mucus in a blurring of the barium deposit The changes

were rapid in onset coming on within three to eight minutes and at their maximum in twenty to thirty minutes and if no food was taken passed off within two hours. The administration of yolk of egg caused more rapid disappearance of the changes. They claim that the alterations in the X ray picture indicate hyperaemia or increased turgor of the mucosa with increased mucous secretion representing the preliminary digestive process.

CLINICAL USE — As increased secretion of mucus might be of some importance it is now believed that the gastric juice contains hydrochloric acid of an initial high acidity which is the same in health and disease. If retained e.g. in a Pavlov pouch this initial acidity falls due mainly to diffusion partly through swallowed saliva and alkaline mucous gastric secretion. Although the pharmacological evidence in favour of bitters is rather sketchy the consensus of clinical opinion is favourable to their employment. It seems clear that they should not be used in health. That they should be administered shortly before food so that any increase produced in appetite or psychic juice may be ready to deal with the early stage of digestion. I do not think they should be administered for long periods but only to start the habit of taking food. They do not depend entirely on the patient's belief in their efficacy. They sometimes stimulate appetite in achylia gastrica without having any effect upon the gastric juice. They have value as appetizers in subnormal nutrition. They should be administered in doses just sufficient to give a strong bitter taste. *Nux vomica* and strychnine have in addition to their bitterness the advantage of increasing the reflex activity of the cord thus tending to increase muscle tone even in the small doses used in tonics. They also increase slightly the local reflex activities of the bowel. This combination of bitter activity and sharpening of reflex activity fully justify their popularity as tonics.

IRON TONICS

Iron preparations are often referred to as tonics but I am not sure that they are rightly so termed. In adequate dosage

they are curative in many forms of anaemia and in my view a tonic is an indirect method of improving health. Iron salts are now given in larger dosage than formerly. This is in keeping with pharmacological findings. In rabbits small doses produce no changes in the bone marrow but with larger doses there is evidence of stimulation of the marrow which becomes denser, and there is a transient increase of young cells, reticulocytes, both in the circulating blood and marrow. With continued administration of medium doses there is evidence of an impairment of the marrow following the initial stage of stimulation, both haemoglobin and red corpuscles showing a definite fall. In rabbits rendered anaemic by bleeding these medium doses of iron caused much more rapid improvement than in untreated anaemic controls and it was noted that in the anaemic animals doses of iron which produced impairment of the marrow in normal animals seemed only to act as stimulants to the marrow.

CLINICAL USE AND DOSAGE—Over forty years ago Stockman suggested that chlorosis then common in young women, was due to a deficient intake of iron in the diet. Recently Davidson investigated the dietary of women in the poorer classes in Aberdeen and found that it contained too little iron. Normally the daily wear and tear of the body consumes about $\frac{1}{2}$ grain of iron which is excreted in the urine. The average good mixed diet contains at least double this amount of iron and is ample for the body's needs. Deficient intake of iron seen especially in women of the poorer classes, leads, during the child-bearing years, to a form of anaemia which is usually termed chronic hypochromic nutritional anaemia or chronic microcytic anaemia. It is essentially due to a diet deficient in iron and is curable by large supplementary doses. This is much more economical than adjusting the diet to include sufficient iron-containing foods, especially now under war conditions. Any iron preparation may be used, e.g. tablets containing 5 grains of ferrous sulphate or ferrous carbonate, thrice daily. A favourite is the iron and ammonium citrate, 30 grains thrice daily, dissolved in chloroform water. The new B.P. preparation, citrated ferrous chloride, is very soluble in

water and is stable. Its dosage is lower, 5 grains thrice daily in solution. Whatever preparation is employed should be given at first in half these doses lest they increase gastric disturbance. They are given after food and gradually increased to the full amount. The treatment is prolonged from four to twelve weeks may be required before the blood picture becomes normal. It is a good rule to continue the full doses for a further four weeks to give the body a reserve store of iron. Then the dosage may be halved. But iron must be taken regularly, as the diet will still remain deficient.

IN INFANTS—Another field in which iron medication is curative is in the hypochromic anaemias of infants. This is often seen in the first two years of life, especially in children who were underweight at birth. But even normal children may show a certain degree of anaemia after any infection. As tablets are unsuitable for infant medication, soluble preparations are used. The iron and ammonium citrate can be dissolved in a little water and added to the food or sweetened with glycerin or chloroform water as a medicine after food. Again adequate dosage is necessary. Davidson recommends as the curative dose for an anaemic infant of three to six months, 3 grains t i d for anaemic children six to eighteen months, 5 to 10 grains t i d. As for adults the general rule of beginning with trial doses of half the full amounts with or after food should be followed and the dose gradually worked up to the full amount.

DIGITALIS

Digitalis may be considered a tonic in so far as restoration of a better circulation will improve the nutrition of all tissues in such measure as is possible by a supply of properly oxygenated blood. Thus all organs in the body may benefit provided they are not too much damaged by the results of the impaired circulation. This is seen most strikingly in the temporary diuresis which results in the early action of digitalis. Provided the kidneys are not damaged by disease, the restoration of an efficient circulation in them re-establishes the necessary difference between the glomerular arteriolar and venous blood-

pressure, and enables the kidneys to do their own usual quota of work and also to overtake their arrears, until the dropsical fluid is removed from the body. In the same way, improvement in the cerebral circulation clears the brain, and the same is true for the lungs. Yet digitalis acts best in auricular fibrillation as a protector of the ventricle, not as a tonic stimulating it.

CONCLUSION

It would be possible to include many other drugs and methods of treatment as evincing temporary tonic action. CO_2 inhalations, causing stimulation of the respiratory centre, induce deeper breathing, more oxygenation of the blood and better functioning of many organs. In recent years a rapid restoration to normal caused by analeptics, in conditions of medullary depression, has interested pharmacologists, but here the action is too rapid to be considered as an instance of the classical conception of a slow acting tonic.

CHAPTER XXIV

VITAMINS IN TREATMENT

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CHAPTER XXIV

VITAMINS IN TREATMENT

THE study of vitamins has reached the second of the two phases usual to advances in therapeutics that arise from laboratory work. At first such discoveries are ignored by clinicians because they are based upon animal experiments, and the pathological conditions in the animals seem rarely, if ever, to appear in man, such was the position in the last war, when vitamins had just been discovered. In the second stage, the advances are accepted with uncritical enthusiasm and some clinicians make extravagant claims for the new panacea, such is the position to-day. Knowledge of vitamins has advanced in recent years with amazing rapidity. Each day now sees one paper published upon the vitamin B complex alone, and each year, for the last five years, one member of that complex has been synthesized. Five years ago awed biochemists gazed through microscopes at valuable traces of a few pure vitamins, now they have large bottles upon their shelves containing several synthetic vitamins. And the clinician, spurred on by optimistic or unscrupulous advertisements has been eager to use pure vitamins in therapy.

It has been realized in the last few years that vitamins do not only cure the rare diseases that the general practitioner usually finds in textbooks—beri-beri, scurvy, pellagra, xerophthalmia, it is now known that slight deficiency causes many signs and symptoms, often difficult to diagnose, and also produces ill health that can only be related to lack of vitamins by employing laboratory methods of diagnosis. Such 'sub-clinical' deficiency has been shown to be common even in times of peace and is likely to become more common as the war progresses. The practitioner now has to be alert to detect mild deficiency, and this article attempts briefly to help him in curing it.

VITAMIN A

There are four fat-soluble vitamins A, D, E and K. Vitamin A, which has been synthesized, belongs to the class of pigments called carotenoids which are widely distributed in nature, and colour buttercups, tomatoes, and lobsters. There are four carotenoids that become converted into vitamin A in the body. The most important dietary sources of these "provitamins", and of vitamin A, are milk, butter, eggs, liver, green vegetables and carrots. The minimum daily requirement of an adult is about 30 I.U. per kilogramme body-weight, and 50 is a safe figure to take in calculating dietary allowances. This amount is contained in a glass of milk, an egg, 25 gm. of butter or margarine, and a moderate helping of green vegetables.

DEFICIENCY — Transformation of the provitamins (carotenes) into vitamin A occurs in the liver, and in diseases of this organ (e.g. cirrhosis) or in diabetes mellitus this transformation is decreased and carotenaemia occurs. Diabetics treated with high carbohydrate diets are particularly prone to deficiency of vitamin A, and during pregnancy or lactation the requirement of the vitamin is increased, patients with steatorrhœa may become deficient through diminished absorption and deficiency also occurs in cases of parenchymatous or obstructive jaundice.

In deficiency of vitamin A atrophy of epithelial tissues and also *night-blindness* occur. Decreased ability for dark adaptation is the earliest sign of deficiency and can be measured photometrically, before the war it occurred not infrequently in this country among apparently healthy people and usually improved immediately with vitamin A therapy. Night-blindness is of outstanding importance now because restriction of fat produces deficiency, and because the black out and night-flying emphasize the disability. In deficiency, epithelial tissues atrophy and become keratinized. This occurs early in the trachea and bronchi and masses of keratinized epithelial cells may block the bronchioles giving rise to bronchiectasis, atelectasis and pneumonia. Keratinization of the cornea and conjunctiva leads to *xerophthalmia*, atrophy of the enamel-forming epithelium of the teeth causes the formation of enamel

to cease, and marked deformities occur as a result of defective formation of dentine. Once epithelial cells have atrophied infection occurs easily, and this is the only connexion between deficiency of vitamin A and infections. It is useless in the therapy of acute infections, or as a prophylactic against colds or influenza, if the diet is adequate.

Therapy—In cases of infection, however, particularly of the respiratory tract, a careful dietary history should be taken, and in cases of steatorrhœa deficiency should be suspected. Patients who complain of night-blindness should receive supplements of the vitamin, if due to deficiency of vitamin A the hemeralopia is usually quickly abolished sometimes within a few hours, but no improvement can be expected in congenital night-blindness (which is dominant) or in riboflavin deficiency (see p. 313). Infants and pregnant or nursing women should receive supplements, as deficiency in them is common, the vitamin has also been used successfully in senile vaginitis. There is no evidence for the claims that it prevents renal calculi, or is beneficial in thyrotoxicosis, demyelination of the spinal cord, or anaemia.

The cheapest and most efficient form of therapy is administration of a good preparation of fish liver oil. *Oleum morrhuae* (B.P.) contains not less than 600 I.U. vitamin A and 85 I.U. vitamin D per gm., the therapeutic dose is 3 to 6 c.c.m. t.d.s. It has a slightly fishy taste and therefore halibut-liver oil is preferable, this contains fifty to one hundred times as much vitamin A, but less vitamin D per dose. A suitable dose is 5 to 10 drops daily for infants, and double this for adults. Supplied in this form the whole daily requirement of vitamin A costs one farthing (retail), and this is the cheapest way of providing the vitamin in the diet. When severe deficiency with xerophthalmia occurs, it should be treated with large doses. Recent work in Aberdeen suggests that some cases of hemeralopia are cured only by massive therapy, such as a single intramuscular injection of 100,000 I.U. There is no danger of overdosage of vitamin A.

VITAMIN D

Vitamin D was first isolated in crystalline form in 1931, and now at least ten different chemical forms of it are known. Only two are important in therapy, calciferol (vitamin D₂) and vitamin D₃, both of which are formed from inactive provitamins by the action of ultra-violet light. The provitamin of calciferol is ergosterol which is the characteristic sterol of yeast and fungi, the provitamin of vitamin D₃ is γ dehydrocholesterol, which is present in animal fats, fish oils, eggs and milk. The conversion of provitamin to vitamin takes place when the skin is exposed to ultra violet light, but deficient sunlight in this country and restricted fats in war time promote deficiency. Fish that contain much body oil, such as sardines and herring are the richest natural sources, eggs, milk and butter or margarine come next, but the amount in them is small and by themselves they are inadequate to supply children with vitamin D. One egg contains about 40 I U, and a pint of summer milk half that, but milk from cows kept indoors contains practically none. Children require about 400 I U daily to prevent rickets—the optimum requirement of adults is probably about 500 I U a day.

DEFICIENCY—Vitamin D increases blood calcium by increasing the absorption from the small intestine and decreasing the excretion into the large intestine. In deficiency of vitamin D the metabolism of bone is faulty and rickets results, deficient calcification of teeth also occurs and leads to caries. Greatest susceptibility to rickets occurs during the first months of life, and as milk is a poor source of vitamin D infants should receive supplements.

THERAPY—Infants tolerate cod liver oil concentrates well and may therefore be given *Oleum morrhuae* (B P) one half to one teaspoonful (200 or 400 I U) daily. *Liquor calciferolis* (B P) contains 3 000 I U vitamin D per gm and no vitamin A, the therapeutic dose is 2 000 to 3 000 I U (0.6 to 1 c cm). It is, however, usual to employ three times these doses in the treatment of rickets, and occasionally doses of 30 000 or more may have to be given. If very large doses (100,000 I U or

more daily) are given, the urine should be examined daily for calcium casts and the serum calcium should be estimated weekly, because toxic doses produce a rise in serum calcium with metastatic calcification. Good results have been claimed with vitamin D therapy in rheumatoid arthritis (Reed *et al.*, 1939).

VITAMIN E

The most active form of this vitamin is a compound *α* tocopherol, which was synthesized in 1938. It is present in vegetable oils, particularly wheat-germ oil. In animals vitamin E plays an essential part in nuclear activities involving chromatin, and in particular is indispensable in those tissues in which rapid cellular proliferation and differentiation occurs (such as the testis in the male and the developing embryo in the female). Also young rats deficient in vitamin E develop paralysis of the hind limbs. Einarson and Ringsted found cord lesions closely resembling tabes dorsalis and progressive muscular atrophy. What relation this work on lower animals bears to disease in man has not been fully elucidated.

Some clinicians have claimed remarkable therapeutic results in habitual abortion and others in threatened abortion. But according to Browne these results are doubtful. Bicknell (1940) claims to have confirmed Einarson's and Ringsted's results clinically, finding vitamin E therapy useful in muscular dystrophies and amyotrophic lateral sclerosis, he used fresh dried whole wheat germ, $\frac{1}{2}$ ounce twice daily. Wechsler has also claimed successful results in amyotrophic lateral sclerosis with *α* tocopherol.

VITAMIN K

Dam in 1929 and subsequently, showed that chickens fed on a diet deficient in fat developed a fatal haemorrhagic tendency owing to a decrease in plasma prothrombin. The coagulability of the blood could be restored by a fat-soluble substance which he called vitamin K. It is present in green vegetables, such as cabbage and spinach, in alfalfa and in decayed fish meal.

THERAPY—It is well known that patients with obstructive jaundice or biliary fistulae may develop a haemorrhagic diathesis owing to diminished clotting power of the blood and this is restored to normal by oral administration of bile salts. It has recently been shown that bile is necessary for the absorption of vitamin K from the gut, and that the vitamin is necessary for the formation of prothrombin in the liver. Parenteral administration of the vitamin is therefore indicated in patients who have no bile in the gut—cases of obstructive jaundice and biliary fistulae, but oral administration of bile salts 1 to 3 gm daily, is often sufficient. It has also been proved that vitamin K therapy is of enormous value in haemorrhagic disease of the newborn (Waddell and Lawson, 1940, Poncher and Kato, 1940). Other indications for therapy are rare. Cases of steatorrhœa, ulcerative colitis, chronic hepatitis, cirrhosis of the liver, nephritis and hypertension are occasionally accompanied by a haemorrhagic diathesis which responds to therapy with the vitamin. But such therapy is useless in haemophilia, thrombocytopenic purpura, and leukaemia. Since the vitamin has been shown to lower the clotting of the blood of apparently healthy persons pre-operative therapy might be tried in cases in which post-operative bleeding must be avoided.

Synthetic compounds (derivatives of naphthaquinone) that have vitamin K activity are available and cheap, some of them are water-soluble. Parenteral administration is advisable and 2 to 4 mgm daily is a reasonable dose.

VITAMIN B COMPLEX

VITAMIN B₁—This the antineuritic vitamin is also called aneurin, thiamin and torulin. It has recently achieved notoriety because of the decision of the Ministry of Food to add synthetic vitamin B₁ to all white flour. Owing to the synthesis of the vitamin four years ago pure preparations are now readily available and it is interesting to see the difference in cost that is brought about by such an achievement. The Ministry of Food seems to be paying about 3s 6d for 1 gm of synthetic vitamin B₁, only five years ago the most efficient way of obtaining 1 gm was to buy £200 worth of yeast and extract the vitamin from

it by a long and costly method. Few common foods are rich in the vitamin. Wholemeal bread is a good source and usually contains about twice as much as brown bread and ten times as much as white. Oatmeal, liver, kidney, pulses, eggs, and pork are all fairly good, milk is a poor source. The optimum intake is probably about 2 mgm. a day, but many factors increase the requirement and it is important to appreciate them in any consideration of therapy.

DEFICIENCY — The requirement is proportional to the body-weight, the total metabolism, and the energy value of the ingested carbohydrate. Therefore deficiency is found in those who are on unbalanced or high-carbohydrate diets (alcoholics, diabetics, patients with gastric ulcers or infants fed on "glucose lemonade"), and those who have increased metabolism (through muscular work or rapid growth, pregnancy, fever or hyperthyroidism). Deficiency is also easily caused by failure of assimilation. The vitamin is unstable in alkali, or in acid in presence of blood, and destruction therefore tends to occur in the gut in persons with achlorhydria, pyloric stenosis, gastric carcinoma, or gastric ulcer, and there may be failure of absorption in cases of diarrhoea, ulcerative colitis, and gastro- or entero-enterostomy. In absence of the vitamin the cells of the body cannot burn carbohydrate fully, and therefore the signs of deficiency appear first in the nervous and cardiovascular systems, because their cells depend for energy predominantly upon the oxidation of carbohydrate. neuritis or cardiac failure therefore may occur.

THERAPY — It is obvious that only the cases of neuritis and cardiac failure that are due to deficiency of the vitamin will respond to therapy with it, and it is unfortunate that fantastic claims have been made for the therapeutic use of vitamin B₁, diseases as dissimilar as lead neuritis, subacute combined degeneration of the cord, disseminated sclerosis, and sciatica have all been alleged to respond. Some at least of the cases of nutritional, "alcoholic," gastogenous, gestational, diabetetic, and "infective" polyneuritis are caused by deficiency of vitamin B₁, but in true cases of infective polyneuritis, and in

most cases of diabetic neuritis, no improvement can be expected with vitamin therapy. Cases of cardiac dilatation and tachycardia without any obvious signs of organic heart disease, and cases of oedema not of cardiac or renal origin and with normal plasma proteins, can reasonably be treated with vitamin B₁. The oedema and cardiac dilatation of wet beri beri respond dramatically to therapy, and this condition occurs occasionally in this country (see Konstam and Sinclair, 1940). The neuritis is quickly cured in the early stages before degeneration of the axis cylinder has occurred, but long-standing cases may obtain little or no improvement. It should be borne in mind that anorexia is an early sign of deficiency of vitamin B₁ and responds rapidly to therapy. Goodhart and I (1940) concluded "that definite deficiency of vitamin B₁ is not uncommon among hospital patients."

Pure vitamin B₁ is readily available for oral or parenteral therapy, and there is no danger of overdosage. In definite cases of deficiency it is wise to start treatment with intramuscular or intravenous injection of very large doses—20 to 50 mgm daily. Later the same amount may be given orally, or the injections decreased to 10 mgm or less daily.

NICOTINIC ACID—The vitamin B₂ complex consists of at least five factors of which four—nicotinic acid, riboflavin, vitamin B₆ and pantothenic acid—have been synthesized, a summary of this complex and of vitamin B₁ will be found elsewhere (Sinclair, 1941). Nicotinic acid is a cheap pyridine derivative, first prepared three-quarters of a century ago. In 1937, it was shown to cure pellagra. This disease is rarely recognized in this country, where it occurs most frequently in patients with ulcerative colitis or in mental hospitals. The main signs are sore ulcerations of the mouth and an ulcerated atrophic tongue of a fiery red mental changes and a characteristic dermatitis. The acute mental symptoms, which vary from slight confusion to delirium or mania, respond dramatically to nicotinic acid usually clearing up overnight, the oral manifestations and the cutaneous erythema disappear in a few days.

THERAPY — The usual dose of nicotinic acid is 500 mgm a day, given by mouth in doses of 50 mgm. It is advisable to divide the daily dose in this way because nicotinic acid, unlike almost all other vitamins, is definitely toxic, large amounts cause flushing, burning and itching of the skin, and increased motility of the stomach.

In treating pellagrins it is important to bear in mind that the disease is usually accompanied by other vitamin deficiencies. Many pellagrins suffer from peripheral neuritis, which is cured by vitamin B₁, many suffer from cheilosis, which is cured by riboflavin. Korsakow's psychosis sometimes accompanies pellagra, and this is believed by some to be due to deficiency of vitamin B₁. Wernicke's encephalopathy, on the other hand, is probably due to deficiency of nicotinic acid. It has recently been shown (King, 1940) that Vincent's disease, or "trench mouth," is due to deficiency of nicotinic acid, the organisms being able to grow only on the tissues that have been damaged by vitamin deficiency. Since this acute ulcerative infection of the mouth and throat was common in the last war, and has appeared during this one the practitioner should keep a watch for the disease and cure it by the oral administration of nicotinic acid.

RIBOFLAVIN — This member of the vitamin B₂ complex was synthesized in 1935, it is present in yeast, milk, eggs and liver, and is destroyed by light. Sebrell first recognized the clinical manifestations of *riboflavinosis*, which consist essentially of cheilosis and seborrhoeic excrescences around the nose. In 1938 Sebrell and Butler fed eighteen women on a purified diet, after about one hundred days ten of the subjects developed the characteristic signs. These begin as a pallor of the mucosa of the lip in the angles of the mouth, soon followed by maceration and then superficial transverse fissures, which may extend on to the skin. At the same time there is a superficial denudation of mucosa, making the lips abnormally red along the line of closure. In addition "there was also seen a fine scaly, slightly greasy desquamation on a mildly erythematous base in the nasolabial folds, on the alæ nasi, in the vestibule of the nose

and on the ears" (Sebrell and Butler, 1939) These lesions were alleviated by synthetic riboflavin, but not by nicotinic acid. Occasionally seborrhœic dermatitis is found on the face and ears and other parts of the body. The tongue is magenta in colour, and not the bright fiery red of nicotinic acid deficiency. Recently Sebrell and his colleagues (Sydenstricker *et al.*, 1940, Kruse *et al.*, 1940) and others have shown that deficiency of riboflavin in man also produces a keratitis, even without lip or tongue lesions. Forty-seven patients with riboflavin deficiency showed slit-lamp evidence of a vascularizing keratitis, accompanied by symptoms of photophobia, dimness of vision, circumcorneal injection and a burning sensation of the eye ball. The conjunctivitis was sometimes accompanied by mydriasis, iritis and corneal opacities. Administration of 5 to 15 mgm of riboflavin produced dramatic improvement. Pock Steen observed similar signs in one hundred patients with sprue and allied disorders in the East Indies, the most frequent symptom was reduced visual acuity in dim light, which was not affected by vitamin A but cured by 1 mgm riboflavin. Johnson and Eckardt (1940) observed that riboflavin was of value in rosacea keratitis. It is apparent therefore that keratitis cheilosis, and twilight-blindness may be caused by riboflavin deficiency. Riboflavin is now becoming easily available for therapeutic use, 3 to 5 mgm a day, administered orally, is the usual dose.

VITAMIN B₆—This vitamin was synthesized in 1940. In rats it prevents an extensive symmetrical dermatitis consisting, histologically, of hyperkeratosis and a great increase in the vascularity of the skin. The disease is alleged to resemble "pink disease" in children, and many regard this as a deficiency disease, there are claims that parenteral administration of vitamin B₁ cures it. These rats also develop a macrocytic anaemia and are prone to have fits.

Deficiency in man has not yet been recognized, although Spies and his colleagues have claimed improvement in the health of four cases of nutritional deficiency, the intravenous administration of vitamin B₆ is alleged to have cured their irritability, nervousness, insomnia, vomiting, weakness, and

reeling gait. It has recently been stated in the U.S.A. that good results have been obtained with vitamin B_6 in the treatment of *paralysis agitans*. If therapy with B_6 is thought to be advisable in a specific case, 20 mgm. intravenously is a reasonable dose to use.

PANTOTHENIC ACID—This vitamin prevents dermatitis in chickens and was synthesized in 1940. It is present in human blood, and according to Spies the amount is decreased in the blood of persons who have deficiency disease, but there are as yet no indications for therapy in man.

Nevertheless, if a patient suffers from deficiency of one member of the vitamin B complex, it is probable that he will be partly deficient in others also. It is therefore advisable to supplement parenteral administration of a single pure vitamin with oral administration of a rich source of the whole complex. Dried brewers' yeast provides such a source, it is easily administered stirred into milk, or in warm water with salt, and about 30 gm. daily is a convenient dose for an adult.

VITAMIN C

Vitamin C, also called ascorbic acid, was synthesized in 1933 and is now cheap. The richest natural sources are oranges, blackcurrants, lemons, grape fruit, tomatoes and raw cabbage, but unfortunately the vitamin is easily destroyed during storing or cooking. Boiling a cabbage in an open vessel causes almost complete destruction, and standing milk on a doorstep in the sun is also fatal. Like vitamin B_1 , vitamin C is rapidly destroyed in alkali, and therefore people with gastric achlorhydria tend to become deficient. The optimum daily intake is probably at least 50 mgm. a day.

DEFICIENCY—Vitamin C is necessary for the formation of the intercellular material of tissue derived from mesenchyme. In its absence the intercellular material of the capillary endothelium is deficient, collagen is not found between the cells of connective tissue, and osteoid tissue in bone and dentine are imperfectly formed. In scurvy the main lesions are therefore found in bones, the teeth and the gums around diseased teeth,

and the capillaries Follicular hyperkeratotic papules are an early sign (Crandon *et al* 1940)

THERAPY —For therapeutic purposes fresh orange juice (which contains about 50 mgm vitamin C per 100 c cm) is admirable, but it is now difficult to obtain, blackcurrant juice can be used instead *Acidum ascorbicum* (B P) is pure crystalline vitamin C, the therapeutic dose is 100 to 250 mgm, and there is no danger of overdosage Large doses should be used in the treatment of scurvy There is no doubt that deficiency of vitamin C lowers resistance to infection and decreases the rate of healing of fractures and wounds, but there is no evidence that the vitamin increases such resistance or healing in the absence of deficiency However, it is known that an enormous number of people ingest sub optimum amounts of this vitamin and therefore supplements should be given when there is a poor dietary history, in chronic infectious diseases (especially tuberculosis), and in pregnancy and lactation

VITAMIN P

In 1936 Szent Gyorgyi claimed that certain plant pigments (flavanones) in particular hesperidin and eriodictyol glucosides, cured some of the symptoms of scurvy and prevented haemorrhages in various diseases He called the factor the vitamin P, but was later unable to confirm his original experiments But others have claimed to have cured patients supposed to have scurvy and also cases of thrombocytopenic purpura with lemon juice, after ascorbic acid had been proved to be ineffective Scarborough (1939) however supported the existence of vitamin P by demonstrating that the increased capillary fragility found in cases of multiple vitamin deficiency is restored to normal by flavanones even when ascorbic acid has failed It is therefore important not to rely too blindly upon ascorbic acid in the treatment of scurvy or of purpura but to correct the dietary error if present and administer lemon juice

CONCLUSION

In the last few years biochemists have made available cheap and pure preparations of the eleven vitamins mentioned above,

they have also shown by laboratory estimations of some of these vitamins in blood or urine, and by other methods, that even in times of peace slight deficiency of vitamins is surprisingly common in our population, and gross deficiency occurs far more often than is usually supposed. These two discoveries provide important opportunities and dangers. The dangers in therapy are two-fold. First, vitamin deficiencies are seldom single, and to treat a case of multiple deficiency with a single pure vitamin is obviously bad therapy. It is therefore important to bear in mind the causes of vitamin deficiencies. A person may partake of a diet that, on paper, appears well-balanced, but the green vegetables may be boiled perhaps in a copper utensil perhaps with soda, and the water which contains what little vitamin escapes destruction is thrown away. Deficiency of water soluble vitamins particularly B₁ and C may therefore result. The person may have achlorhydria or take alkalis, and thereby certain vitamins become destroyed, or diarrhoea may prevent absorption, particularly of water-soluble vitamins in cases of ulcerative colitis and of fat-soluble vitamins in cases of steatorrhoea. And many other factors may produce deficiency in cases in which it would not normally be suspected. Rich children fed on highly refined foods and stuffed with sweets may fare far worse than poor brats eating scraps. Therefore it is important in patients with deficiency to investigate the cause and correct it. The second danger arises from the prominence vitamins now receive and the unscrupulous way in which certain manufacturing firms press them as a panacea. I have seen a case of diabetic neuritis diagnosed as deficiency of vitamin B₁ and treated as such, to the exclusion of appropriate therapy.

The opportunities lie even more in prevention than cure. Some airmen manning fighter aircraft at night are renowned for being quicker than others at detecting enemy bombers. What part does sufficiency and deficiency of vitamin A or riboflavin play there? With AA gunners, first-aid units, wardens, roof-spotters, firemen, searchlight crews and the Home Guard on duty at night, dark-adaptation becomes increasingly important. Vitamin B₁ is alleged to decrease muscular fatigue when given

in excess to apparently healthy people how much does slight deficiency of this vitamin decrease the output of factory workers engaged overtime, and what part does vitamin deficiency play in the "air-tiredness" of airmen frequently engaged on long flights? Although the answers to these questions are not known, the solution to the general problem they raise is available. It is not merely to fortify common foodstuffs—bread and margarine—with three vitamins. In many cases synthetic vitamins are cheaper than those in natural foodstuffs, in other cases "artificial" foods such as dried brewers' yeast or halibut-liver oil, provide the cheapest sources. Sufficient is now known about human requirements of the most important vitamins to provide the minimum daily dose requirement of at least half a dozen vitamins together with essential salts in the form of, say, a biscuit at comparatively trivial cost. In 1938 the people in the USA spent over \$100 000 000 on vitamin preparations manufactured or sold through pharmaceutical channels, in this country at the present time the man-consumption is probably higher. If the Government took the lead by providing a vitamin-biscuit free, or at low cost, the return in output and efficiency might well be incalculable. There is nothing unnatural in such a step. Salt is good, and sodium chloride is added by everyone to his diet because natural food contains insufficient, and no one complains when iodides are also added. Vitamins are better, and why should it not therefore be ensured that everyone gets sufficient of the vitamins he is known to need? But that is modern—or it is hoped not distant—prophylaxis, in the meantime, the practitioner must be alert to detect and correct slight degrees of deficiency which are known to be common that is modern therapeutics.

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APPENDIX

APPENDIX

THE following list of drugs and their substitutes or equivalents is reproduced by kind permission of the Controller of H M Stationery Office. It is taken from 'Economy in the Use of Drugs in War Time' as prepared by the Therapeutics Requirements Committee of the Medical Research Council (H M Stationery Office Price 3d.)

The drugs are classified as follows —

A Drugs which are at present either regarded as essential or are readily available

B Drugs which are essential for certain purposes but not for others, and in the use of which strict economy should be observed

C Drugs which are not essential and do not justify importation or manufacture for home use in war time

It should be borne in mind that drugs classified as 'B' should be prescribed with great care. For non-essential 'C' or restricted use "B" drugs, substitutes procurable in this country are indicated

Drug	Classification	Substitute or Equivalent and Remarks
Acacia	A	
Acaprin	C	Pirevan is identical
Acetanilidum	C	Substitutes Acetylsalicylic acid or phenacetin
Acetarsol	A	
Acetylcholine	C	
Acetonum	B	Under Government control
Acidum Aceticum	B	
Acidum Acetylsalicylicum	A	
Acidum Ascorbicum	A	
Acidum Benzoicum	B	
Acidum Boricum	B	Boric acid in Boric Lint is wasted Reserve for Cataplasma Kaolini and eye lotions In dermatological practice saline compresses may be used instead of boric fomentations and for dusting powders boric acid may be replaced by zinc oxide, magnesium trisilicate or kaolin
Acidum Citricum	B	Manufacture under Government control

Drug	Classification	Substitute or Equivalent and Remarks
Acidum Chromicum (Chromii Trioxidum)	A	
Acidum Glycerophosphoricum and its salts	C	No substitute necessary
Acidum Hydrobromicum	C	
Acidum Hydrochloricum	A	
Acidum Hydrocyanicum	A	
Acidum Lacticum	B	
Acidum Mandelicum	A	
Acidum Nicotinicum	A	
Acidum Nitricum	B	
Acidum Oleicum	B	
Acidum Phosphoricum	A	
Acidum Salicylicum	A	
Acidum Sulphuricum	A	
Acidum Tannicum	A	
Acidum Tartaricum and its salts	B	Raw material is imported. Production within the Empire should be encouraged
Aconitum	C	Countries of origin Germany, Switzerland, France. Importation unnecessary. Substitute Benzo-caine for local application
Acriflavina	A	
Adeps Benzoinatus	B	Under Government control
Adeps Lanæ	A	Under Government control
Adrenalina, its salts and esters	A	
Aether	A	
Athylenum	C	
Aethylis Chloridum	A	
Aethylmorphinæ Hydrochloridum	A	
Agar	B	Substitute Ispaghula. Agar should be reserved for bacteriological media. Production within the Empire should be encouraged
Alcohol	B	Many tinctures can be replaced by concentrated preparations. Economy is essential
Alcohol Isopropylicum	C	
Allobarbitonum	A	
Aloc	A	
Alounum	A	
Alumen	A	Use ammonium alum only
Aluminu Acetas	A	Not to be made from potassium alum
Aluminu Hydroxidum	A	Not to be made from potassium alum
Amidopyrina	C	Substitutes Acetylsalicylic acid, phenacetin
Aminophylline	A	See Theophyllina cum Aethylenediamina

Drug	Classification	Substitute or Equivalent and Remarks
Ammonii Carbonas	A	
Ammonii Chloridum	A	
Ammonii Phosphas Acidus	A	
Amphetamina	A	
Amylis Nitris	A	
Amylocainæ Hydrochloridum	A	
Amylum	B	Under Government control In dermatological practice substitute saline compresses for starch poultices and for powders see remarks under boric acid
Anæsthesin	—	Benzocaine is identical
Anethum	A	Production in the United Kingdom should be encouraged
Aneurinæ Hydrochloridum	A	
Aniline Dyes	A	These include Bordeaux B brilliant green crystal violet, fuchsin, gentian violet, malachite green, methyl violet and scarlet red
Anisum	A	
Antimony Compounds	A	
Apomorphinæ Hydrochloridum	A	
Areca	A	
Arecolinæ Hydrobromidum	A	
Argenti Nitras	A	
Argentoproteinum	A	
Arseni Trioxidum	A	
Atebrin	—	Mepacrinæ Hydrochloridum is identical
Atophan	—	Cinchophenum is identical
Atoxyl	—	Sodii Ammarsonas is identical
Atropina and its salts	A	
Atropinæ Methylnitras	A	
Aurantii Cortex	B	Countries of origin Spain Sicily, Malta Production within the Empire should be encouraged Limited supplies are available from the Empire at present
Avertin	—	Bromethol is identical
Balsamum Peruvianum	A	
Balsamum Tolutanum	C	Countries of origin Columbia, S America Importation unnecessary in war time Production within the Empire should be encouraged
Barbitonum	A	
Barbitonum Solubile	A	
Barn Sulphas	A	
Bayer 205	—	Sutaminum is identical
Belladonnae Folium	A	

Drug	Classification	Substitute or Equivalent and Remarks
Belladonnae Radix	A	
Benzaminae Hydrochloridum	B	
Benzaminae Lactas	B	
Benzedrine	—	Amphetamine is identical
Benzocaina	A	
Benzoinum	A	Production within the Empire should be encouraged
Benzylis Benzoas	A	
Betaina Hydrochloridum	C	
Betanaphthol	A	
Bismuthum Precipitatum	A	
Bismuth salts	B	Reserve for the treatment of syphilis and tropical diseases Substitutes (for gastro-intestinal conditions) Aluminium hydroxide, chalk, kaolin magnesium trisilicate
Bismuth Salicylas	B	Reserve for the treatment of syphilis and tropical diseases Substitutes (for gastro-intestinal conditions) Activated charcoal kaolin
Borax	B	In dermatological practice reserve for Unguentum Aquosum Glycenn of borax and honey of borax may be replaced by aqueous solutions of aniline dyes in the treatment of thrush
Bromethol	A	
Bromides	B	Strict economy is necessary
Bromoformum	C	
Buchu	C	Country of origin S Africa Importation is unnecessary Substitutes Hexamine, mandelic acid scoparium, sulphanilamide
Caffeina	B	Omit from compound tablets such as compound aspirin tablets
Caffeina et Soda Benzoas	B	Amphetamine (benzedrine), leptazol (cardiazol) and nukethamide (coramine) are partial substitutes
Calamina	A	
Calciferol	A	
Calcii Carbonas	A	
Calcii Chloridum	A	
Calcii Gluconas	A	
Calcii Hydroxidum	A	
Calcii Lactas	A	
Calcii Sulphas Exsiccatus	A	
Calumba	C	Country of origin E Africa (Mozambique) Production within the Empire should be encouraged Substitute Quassia
Calx Chlorinata	A	

Drug	Classification	Substitute or Equivalent and Remarks
Camphora	A	Production within the Empire should be encouraged
Cannabis Indica	C	Countries of origin India, S Africa, Zanzibar
Cantharis }	C	Countries of origin U S S R, Spain
Cantharidinum }		Hungary, China Importation unnecessary in war time Production within the Empire should be encouraged Substitute Sinapis
Capsicum	B	Countries of origin Nigeria Sierra Leone, E India Restrict use of capsicum to manufacture of capsicum wool Substitute Sinapis Colonial varieties of capsicum may be obtainable
Carbacholium	A	
Carbamide (Urea)	A	
Carbo	A	
Carbo Activatus	A	
Carbonei Dioxidum	A	
Carbonei Tetrachloridum	A	
Carbromalum	B	
Cardamomum	A	
Cardiazol	—	Leptazolum of home manufacture is identical
Carum	C	Countries of origin Holland Germany Some English caraway is available and its production should be encouraged Substitute Anethum (dill)
Caryophyllum	B	Countries of origin E India Zanzibar, Pemba Madagascar Reserve for distillation of the oil
Cascara Sagrada	B	Countries of origin Canada, U S A Production within the Empire should be encouraged
Cassia	C	Country of origin China Importation unnecessary
Catechu	A	
Cera	A	
Chiniofonum	A	
Chloralis Hydras	A	
Chloramina	A	
Chlorbutol	A	
Chlorinated Xylenol	A	Parachloromethylxylenol
Chlorocresol	A	Parachloromethylcresol
Chloroformum	A	
Chondrus	A	Production in the United Kingdom should be encouraged
Chromu Trioxidum (Acidum Chromicum)	A	

Drug	Classification	Substitute or Equivalent and Remarks
Chrysarobinum	B	Production within the Empire should be encouraged Substitute Diphenyl
Cinchona	B	Importation should be restricted to supplies required for the manufacture of quinine The use of cinchona as a bitter should be discouraged Production within the Empire should be encouraged
Cinchophenum	A	
Cinnamomum	A	
Coca	A	Production within the Empire should be encouraged
Cocaina and its salts	A	
Coccus	C	Countries of origin Canary Islands Importation is unnecessary Substitute Solution of Bordeaux B Other good colours are available
Codeina	A	
Colchici Corraus	A	Production in the United Kingdom should be encouraged
Colchici Semen	A	
Colocynthis	A	Production within the Empire should be encouraged
Colophonium	A	
Copaiba	C	Country of origin Northern S America Importation unnecessary Substitutes Hexamine, mandelic acid scoparium, sulphuramamide
Coramine	-	
Coriandrum	C	Nikethamide is identical Countries of origin Morocco, U.S.S.R., India Central Europe Importation unnecessary Substitute Cardamomum
Corpus Luteum and its preparations	B	
Creosotum	A	Production within the Empire should be encouraged
Cresol	A	
Creta	A	
Cubeba	C	Country of origin Malay Archipelago Importation unnecessary Substitutes Hexamine, mandelic acid, scoparium sulphuramamide
Cupri Sulphas	A	
Cusso	C	Country of origin N.E. Africa Importation unnecessary Substitutes Carbon tetrachloride, male fern
Cyclopropanum	B	
Derris	A	

Drug	Classification	Substitute or Equivalent and Remarks
Desoxycorticosterone and its esters	B	Extract of suprarenal cortex is in free supply
Dextrosum	B	Under Government control Reserve for injection
Dextrosum Monohydratum	B	Under Government control Strict economy is essential
Dial	—	Allobarbitonum is identical
Diamorphinæ Hydrochloridum	A	
Digitalis	A	
Digoxinum	A	
Diodone	A	
Dionine	—	Δ Ethylmorphinæ Hydrochloridum is identical
Dithranol	A	Dioxyanthranol
Doryl	—	Carbacholium is identical
Emetina and its salts	A	See Ipecacuanha
Ephedra	A	Production within the Empire should be encouraged
Ephedrina and its salts}	A	
Ergot Alkaloids	A	Production within the Empire should be encouraged
Ergota	A	
Erythritylus Tetranitras Dilutus	C	
Eumydriu	—	Atropinæ Methylnitras is identical
Euphyllin	—	Theophyllina cum Δ Ethylenediamina (aminophylline) is identical
Evipan and Evipan Sodium	—	Hexobarbitonum and Hexobarbitonum Soluhile are identical
Extractum Fellis Bovini	A	
Extractum Hepatis Liquidum (and preparations of the active principles of liver)	B	Importation of liver is under Government control Injection therapy is more economical and effective than administration by mouth Desiccated stomach may be substituted for liver for oral administration
Extractum Malti	B	Under Government control
Extractum Parathyroidei (and parathyroid preparations for parenteral injection)	B	
Extractum Pituitari Liquidum (and preparations for intranasal insufflation)	A	
Extractum Suprarenali Corticis	A	
Extractum Thyroidei Liquidum	A	
Ferm Arsenas	C	Substitute: Ferrous sulphate with arsenic

Drug	Classification	Substitute or Equivalent and Remarks
Ferri Carbonas	A	
Ferri Carbonas Saccharatus	B	Restrict to children
Ferri et Ammonii Citras	B	Not the most economical form of iron, ferrous sulphate is cheaper
Ferri et Manganu Citras	C	Substitute Ferrous sulphate
Ferri et Quininæ Citras	C	Substitute Ferrous sulphate
Ferri et Potassu Tartras	C	Substitute Ferrous sulphate
Ferri et Strychninæ Citras	C	Substitute Ferrous sulphate with strychnine
Ferri Glycerophosphus	C	Substitute Ferrous sulphate
Ferri Hypophosphus	C	Substitute Ferrous sulphate
Ferri Lactas	B	
Ferri Perchloridum	A	
Ferri Subchloridum Citratum	B	Not the most economical form of iron ferrous sulphate is cheaper
Ferri Sulphas	A	
Ferrum Redactum	A	
Ficus	C	Therapeutic value doubtful
Filix Mas	B	Reserve for use when other anthelmintics are contraindicated. Production in the United Kingdom should be encouraged
Fluoresceinum Soluble	A	
Foeniculum	C	Production in the United Kingdom should be encouraged
Fouadin	—	
Galla	B	
Gelatinum	A	
Gelsemium	C	Country of origin U.S.A. Importation unnecessary Substitutes Synthetic analgesics
Gentiana	C	Countries of origin France Germany Spain Almost unobtainable Substitute Quassia Production within the Empire should be encouraged
Germanin	—	
Glucosum	B	Subarabinum is identical Under Government control Strict economy is essential
Glycerinum	B	Substitutes are under investigation
Glycerylis Trinitras	A	
Glycyrrhiza	B	Countries of origin Spain Sicily, Italy Iraq U.S.S.R. Production within the Empire should be encouraged
Gold Compounds	A	
Guaiacol	A	
Hamamelis	C	Country of origin U.S.A. Production within the Empire should be encouraged Substitute Tannic acid
Heparin	A	
Hexobarbitonum	A	

Drug	Classification	Substitute or Equivalent and Remarks
Hexobarbitonum Solubile	A	
Hexamina	A	
Hexylresorcinol	A	
Histamina Phosphas Acidus	A	
Homatropina and its salts	A	
Hydrargyrum	B	
Hydrargyrum Ammoniatum	B	
Hydrargyri Iodidum Rubrum	B	
Hydrargyrin Oxidum Flavum	B	
Hydrargyrin Oxycyanidum	B	
Hydrargyrin Perchloridum	B	Substitute A phenolic antiseptic of the chlorinated phenol type.
Hydrargyrin Subchloridum	B	
Hyoscyamus muticus	A	For manufacture of atropine Production within the Empire should be encouraged
Hyoscyamus niger	A	Production in the United Kingdom should be encouraged
Hyoscina and its salts	A	
Ichthammol	B	
Inducarminum	A	
Injectio Ferrini	C	Substitute Ferrous sulphate by mouth
Injectio Hepatis	B	
Insulinum	A	
Insulinum Protaminatum cum Zincu	A	
Iodoformum	A	
Iodophthaleinum	A	
Iodoxylum	A	
Iodium	B	Production at home and within the Empire should be encouraged Adequate supplies are available, but, owing to shortage of alcohol the use of alcoholic solutions of iodine must be greatly restricted Substitutes Aqueous solutions of iodine acriflavine, brilliant green, crystal violet, proflavine, and trinitrophenol
Ipecacuanha	B	Galenical preparations of ipecacuanha as expectorants and emetics are not essential and the crude drug should preferably be reserved for the manufacture of emetine Production within the Empire should be encouraged
Ispaghula	A	
Jaborandi	B	Reserve for the manufacture of pilocarpine Production within the Empire should be encouraged.

Drug	Classification	Substitute or Equivalent and Remarks
Jalapa Jalapæ Resina}	B	Reserve for veterinary use Countries of origin Mexico India Substitute Colocynth
Kaolinum	A	
Kino	A	
Krameria	C	Country of origin Peru Production within the Empire should be encouraged Substitute Tannic acid
Lactosum	B	
Lavulosum	B	
Lead salts	A	
Linum	C	Substitute Cataplasma Kaolini for poultices
Leptazolum	A	
Liquor Calcis Sulphuratus	A	
Liquor Cresolis Saponatus	A	Not to be made with potassium hydroxide
Liquor Ferri Perchloridi	A	
Liquor Formaldehydi	A	
Liquor Glyceris Trinitatis	A	
Liquor Hydrogenii Peroxidi	A	
Liquor Picis Carbonis	A	
Liquor Vitaminæ A Concentratus	B	
Liquor Vitaminæ D Concentratus	B	
Liquor Vitaminorum A et D Concentratus	B	
Lobelia	C	Country of origin Eastern U.S.A Production within the Empire should be encouraged Substitute Stramonium
Lobelina	C	Substitutes Nikethamide leptazol
Luminal and Luminal Sodium	—	Phenobarbitonum and Phenobarbitonum Solubile are identical
Magnesii Carbonas	A	
Magnesii Chloridum	B	Reserve for veterinary use
Magnesii Oxydum	A	
Magnesii Sulphas	C	Substitute Sodium sulphate of which very large supplies are available
Magnesii Trisilicas	A	
Medinal	—	Barbitonum Solubile is identical
Mel	B	Under Government control
Menthol	A	Production within the Empire should be encouraged
Mepacrinæ Hydrochloridum	A	
Mepacrinæ Methanesulphonas	A	
Mersalylum	A	
Methylis Salicylas	A	
Methylsulphonol	C	

Drug	Classification	Substitute or Equivalent and Remarks
Methylthioninæ Chloridum	A	
Morphina and its salts	A	
Myosalvarsan	—	Sulpharsphenamina is identical
Nembutal	—	Pentobarbital Sodium is identical
Neorsphenamina	A	
Nicotinamidum	A	
Nikethamidum	A	
Nitrogenu Monoxidum	A	
Novocaine	—	Procainæ Hydrochloridum is identical
Nux Vomica	A	
Oestradiol Oestriol, Oestrone and their esters	B	
Oleum Abietis	C	Country of origin North-east U.S.S.R. Importation unnecessary Substitute any oil of pine
Oleum Amygdalæ	C	Production within the Empire should be encouraged All vegetable oils and fats are under Government control Arachis and other vegetable oils may be used if available
Oleum Anethi	A	Production within the Empire should be encouraged
Oleum Anisi	A	Production within the Empire should be encouraged
Oleum Arachis	B	
Oleum Cadinum	A	Production within the Empire should be encouraged
Oleum Camphoræ Rectificatum	C	Substitute Oleum Terebinthinae See Camphora
Oleum Cardamomi	C	Unnecessary
Oleum Cari	C	See Carum
Oleum Caryophylli	A	
Oleum Chenopodii	B	In Great Britain reserve for veterinary use Substitutes Carbon tetrachloride thymol Production within the Empire should be encouraged
Oleum Cinnamomi	A	See Cinnamomum
Oleum Crotonic	C	Unnecessary
Oleum Eucalypti	A	
Oleum Gaultheriæ	C	Substitute Methyl salicylate
Oleum Gossypii Seminis	B	
Oleum Hippoglossi	B	
Oleum Hydnocarpi	A	
Oleum Iodisatum	A	
Oleum Limonius	A	Production within the Empire should be encouraged
Oleum Lini	B	Under Government control Reserve for internal use in veterinary practice

Drug	Classification	Substitute or Equivalent and Remarks
Oleum Menthae Piperitae	A	Production within the Empire should be encouraged
Oleum Morrhuae	B	Under Government control Substitute Oleum Vitaminatum and veterinary vitaminized oils as applicable to relieve scarcity
Oleum Olivae	B	Under Government control Arachis and other suitable vegetable oils are recognized as substitutes in official preparations
Oleum Rapae	B	Reserve for external use in veterinary practice
Oleum Ricini	A	
Oleum Santali	C	Country of origin India Importation unnecessary Substitutes Hexamine mandelic acid scoparium sulphuramide
Oleum Sesami	B	See under Oleum Amygdale
Oleum Terebinthinae	A	Production within the Empire should be encouraged
Oleum Theobromatis	A	
Oleum Vitaminatum	A	
Opium	A	
Orthocaina	A	
Oxygenium	A	
Pamaquinum	A	
Pancreatinum	A	
Papainum	A	
Paraffinum Liquidum	B	Under Government control Its use should be discouraged
Paraffinum Molle	B	Under Government control
Paraldehydum	A	
Parathyroideum	B	
Pelletierinae Tannas	C	Countries of origin Mediterranean countries Importation unnecessary Substitutes Carbon tetrachloride male fern
Pentobarbital Sodium	A	
Pepsinum	A	
Perabrodil	—	Diodone is identical
Phemutonum	A	
Phenacetinum	A	
Phenazonum	C	Substitutes Acetylsalicylic acid phenacetin
Phenobarbitonum	A	
Phenobarbitonum Solubile	A	
Phenol	A	
Phenolphthaleinum	A	
Phenothiazine	A	
Physostigmina and its salts	A	
Physostigmine Salicylas	A	

Drug	Classification	Substitute or Equivalent and Remarks
Pilocarpina and its salts	B	Substitute Physostigmine and its salts for most purposes
Pirevan	A	
Pituitarium	B	Including anterior lobe extracts
Pix Carbonis Preparata	A	
Pix Liquida	A	
Plasmoquin	—	Pamaquium is identical
Plumbi Acetas	A	
Plumbi Monoxidum	A	
Podophylli Resina	B	Restrict to Indian Podophyllum
Potassa Sulphurata	C	Substitutes Sulphur ointment, solution of sulphurated lime
Potassu Bicarbonas	C	Substitute Sodium bicarbonate
Potassu Bromidum	C	Substitute Sodium bromide
Potassu Chloras	C	Not essential
Potassu Citras	C	Substitute Sodium citrate
Potassu Hydroxidum	C	Substitute Sodium hydroxide
Potassu Iodidum	C	Substitute Sodium iodide
Potassu Nitras	C	Not essential
Potassu Permanganas	C	Substitutes Solutions of other permanganates, other antiseptics
Potassu Tartras Acidus	B	See under Acidum Tartaricum
Procaine Hydrochloridum	A	
Prolavina	A	
Prolactin	B	
Prominal	—	Phemutonum is identical
Prontosil Album	—	Sulphamylamidum is identical
Protargol	—	Argentoproteinum is identical
Psyllium	C	Countries of origin Mediterranean countries Production within the Empire should be encouraged Substitute Ispaghula
Pyroxylnum	A	
Quassia	A	
Quillaja	B	Countries of origin Chile, Peru, India
Quinidina Sulphas	A	
Quinine salts	A	
Resorcinol	A	
Rheum	A	Production of <i>Rheum palmatum</i> in the Empire should be encouraged
Saccharinum Soluble	A	
Salicinum	C	Substitute Sodium salicylate
Salol	C	Unnecessary
Salyrgan	—	Injectio Mersalyl is identical
Santoninum	B	Countries of origin U S S R, Kashmir Importation difficult Production within the Empire should be encouraged Substitutes Hexylresorcinol, phenothiazine
Scammonium	C	Unnecessary Substitute Indian podophyllum.

Drug	Classification	Substitute or Equivalent and Remarks
Scilla	C	Country of origin Sicily Production within the Empire should be encouraged Substitutes Urinea (Indian squill) and other expectorants
Scoparum	A	
Senega	C	Countries of origin Canada and U.S.A. Importation unnecessary Substitutes Ammonium carbonate, ammonium bicarbonate, ammonium chloride
Senna	A	
Sera and Vaccines —		
Antitoxinum Diphthericum	A	
Antitoxinum Cædematiens	A	
Antitoxinum Staphylocicum	A	
Antitoxinum Streptococcum	A	
Antitoxinum Tetanicum	A	
Antitoxinum Vibriosepticum	A	
Antitoxinum Welchicum	A	
Serum Antianthracum	A	
Serum Antidysentericum (Shiga)	A	
Serum Antimeningococcum	A	
Serum Antipneumococcum I	A	
Serum Antipneumococcum II	A	
Toxum Diphthericum Calefactum	A	
Toxum Diphthericum Detoxicatum	A	This includes Diphtheria toxoid diphtheria toxoid antitoxin mixture, diphtheria toxoid antitoxin floccules, and alum precipitated toxoid
Toxum Diphthericum Diagnosticum	A	
Toxum Staphylococcum	A	
Toxum Streptococcum Diagnosticum (Scarlatina)	A	
Toxum Tetanicum Detoxicatum	A	
Tuberculinum Pristinum	A	
Vaccinum Choleracum	A	

Drug	Classification	Substitute or Equivalent and Remarks
Sera and Vaccines (continued) —		
Vaccinum Pertussis	A	
Vaccinum Pestis	A	
Vaccinum Staphylococcum	A	
Vaccinum Typho-paratyphosum	A	
Sinapis	A	
Soaps	A	Potash should not be used in the manufacture of soaps
Soda Lime	A	
Sodu Aminarsonas	A	
Sodu Benzroas	B	
Sodu Bicarbonas	A	
Sodu Bromidum	B	
Sodu Carbonas	A	
Sodu Chloridum	A	
Sodu Citras	B	See under Acidum Citricum
Sodu Diphenylhydantoinas (Dilantinum Solubile)	A	
Sodu Iodidum	A	
Sodu Lactas	B	Reserve for use as a glycerin substitute
Sodu Nitris	A	
Sodu Phosphas	A	
Sodu Phosphas Acidus	A	
Sodu et Potassu Tartras	B	See under Acidum Tartaricum
Sodu Salicylas	A	
Sodu Sulphas	A	
Sodu Tauroglycocholas	C	Substitute Extract of Ox Bile
Sodu Thiosulphas	A	
Sparteina	C	
Spiritus Ætheris Nitrosi	B	Substitute Concentrated solution of ethyl nitrite
Spiritus Methylatus Industrialis	B	Under Government control
Stannum	A	
Stanni Oxidum	A	
Stibophenum	A	
Stilboestrol	A	
Stramonium	A	Production in the United Kingdom should be encouraged
Strophanthus	C	Countries of origin Mozambique Nyasaland Importation unnecessary Substitute Digitalis
Strychnina and its salts	A	
Styrax	B	Country of origin Asiatic Turkey Production within the Empire should be encouraged Wanted for compound tincture of benzoin.

Drug	Classification	Substitute or Equivalent and Remarks
Sucrosom	B	Under Government control
Sulphamalamidum	A	
Sulphapyridinum	A	
Sulpharsphenamina	A	
Sulphathiazole	A	
Sulphonal	C	
Sulphur	A	
Suraminum	A	
Syrups	B	The use of all syrups should be discouraged
Syrupus Ferri Phosphatis Compositus	B	Reserve for children
Syrupus Ferri Phosphatis cum Quinina et Strychnina	C	Substitute Tablets of Easton's Syrup
Talcum Purificatum	C	Raw material imported. For substitutes see under Acidum Boricum
Tamarindus	C	Contries of origin India Burma W Indies Importation unnecessary
Taraxacum	C	Importation unnecessary in war time Production in the United Kingdom should be encouraged
Theobromina	A	
Theobromina et Soda Salinas	A	
Theophyllina	A	
Theophyllina cum Ethyl enediamina	A	
Thymol	A	Production within the Empire should be encouraged
Thyroxideum	A	
Thyroxin sodium	A	
Tinctures	B	Many tinctures can be replaced by concentrated preparations Economy is essential
Totauina	A	
Tragacantha	A	Production within the Empire should be encouraged Methyl cellulose and similar synthetics may be tried as substitutes
Trinitrophenol	A	
Tryparsamidum	A	
Urea	A	
Urginea	B	Importation difficult in war time Iodoxylinum is identical
Uroselectan B	B	Production in the United Kingdom should be encouraged
Valeriana	—	Barbitonum is identical
Veronal	—	
Ventriculus Desiccatus	A	

Drug	Classification	Substitute or Equivalent and Remarks
Vitamins		— See Acidum Ascorbicum Aneurinae Hydrochloridum Calciferol Liquor Vitaminum A Concentratus Liquor Vitaminum D Concentratus Liquor Vitaminorum A et D Concentratus Acidum Nicotinicum Oleum Hippoglossi Oleum Morrhuae Oleum Vitaminatum
Yatren		— Chinofonum is identical
Zinci Carbonas	A	
Zinci Chloridum	B	
Zinci Oleostearas	B	
Zinci Oxidum	A	
Zinci Sulphas	A	
Zingiber	A	If the official variety is scarce supplies from other sources e.g. Africa should be permitted

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